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1. Fianerty, F. A., Jr.: The Value of Rauwolfia Serpentina in the Hypertensive Patient, Am. J. Med. 17:689 (Nov.) 1954.
2. Moyer, J. H., in discussion of Galen, W. P., and Duke, J. E.: Outpatient Treatment of Hypertension with Hexamethonium and Hydralazine, South. M. J. 47:858 (Sept.) 1954.
3. Livesay, W. R.; Moyer, J. H., and Miller, S. I.: Treatment of Hypertension with Rauwolfia Serpentina Alone and Combined with Other Drugs; Results in Eighty-Four Cases, J.A.M.A. 155:1027 (July 17) 1954.

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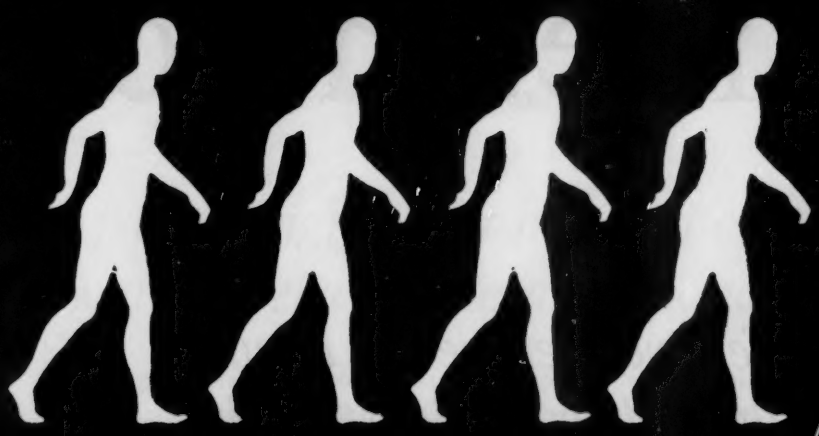

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1. Winsor, T., Humphreys, P.: Angiology *3*:1 (Feb.) 1952.
2. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.
3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.
4. Russek, H. I., *et al.*: Am. J. M. Sc. *229*:46 (Jan.) 1955.

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(1) Dordick, J. R., and Gluck, E. J.: Preliminary clinical trials with metacortandracin in rheumatic diseases. Comparative antirheumatic potency, metabolic activity and hormonal properties, J.A.M.A., in press. (2) Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: J.A.M.A. *157*:311, 1955. (3) Barach, A. L.; Bickerman, H. A., and Beck, G. J.: Clinical and physiological studies on the use of metacortandracin in respiratory disease. I. Bronchial asthma, Dis. Chest, in press. (4) Schwartz, E.: Personal communication.

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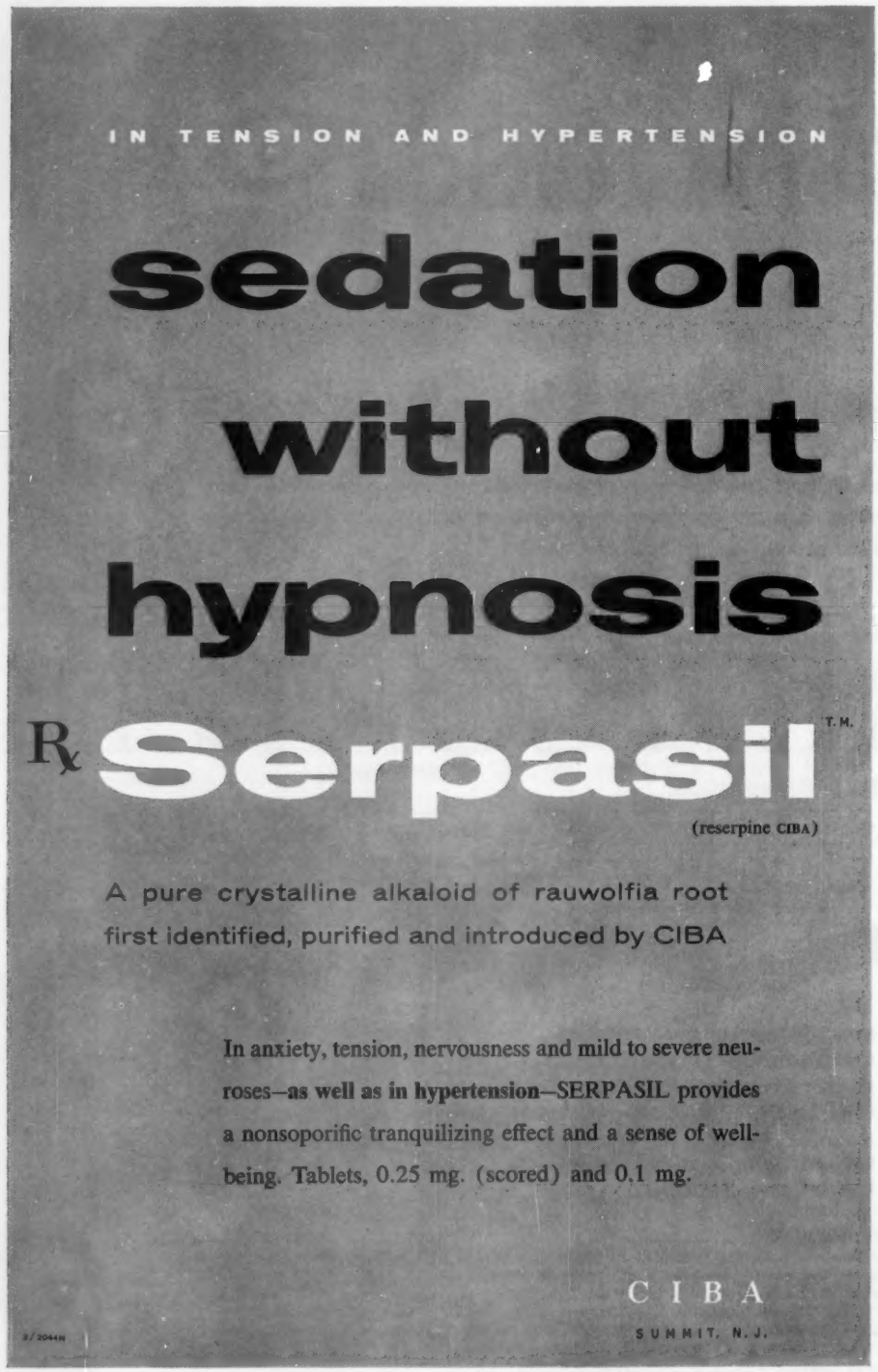
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1. Burke, B.S. and Stuart, H.D.: Nutrition requirements during pregnancy and lactation. J.A.M.A. 132:119 (May 8) 1948.

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References: 1. J.A.M.A. 149:1188, 1952. 2. Gout and Gouty Arthritis, Modern Medical Monographs, 7, New York, Grune & Stratton, 1953, p. 80.

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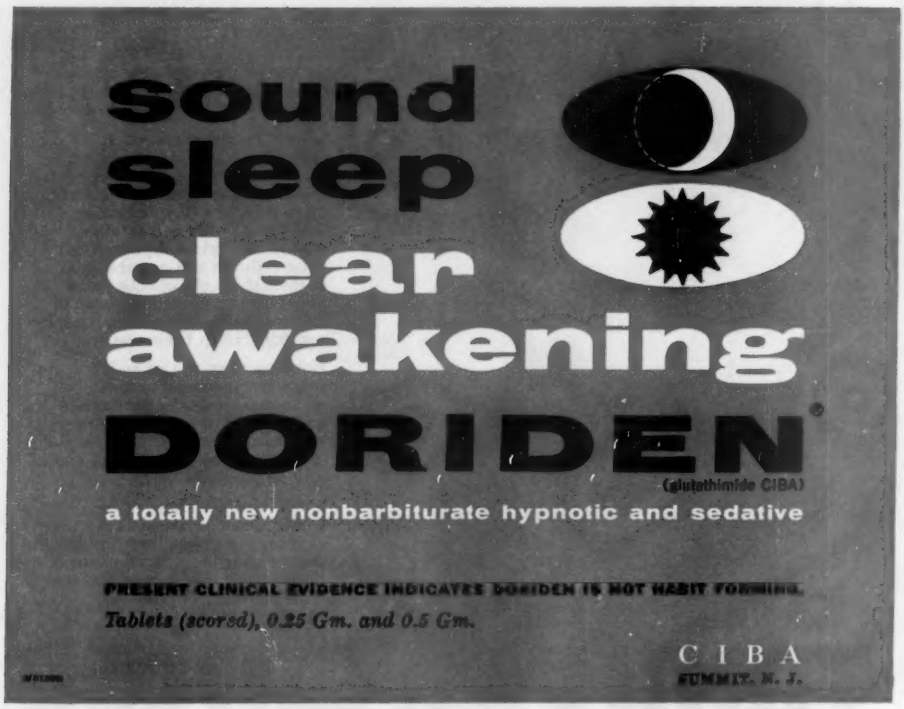

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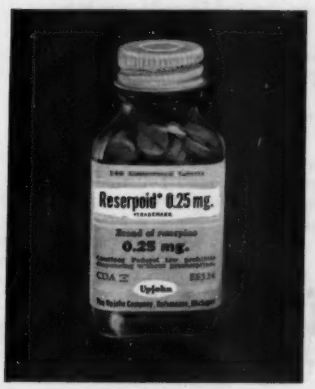

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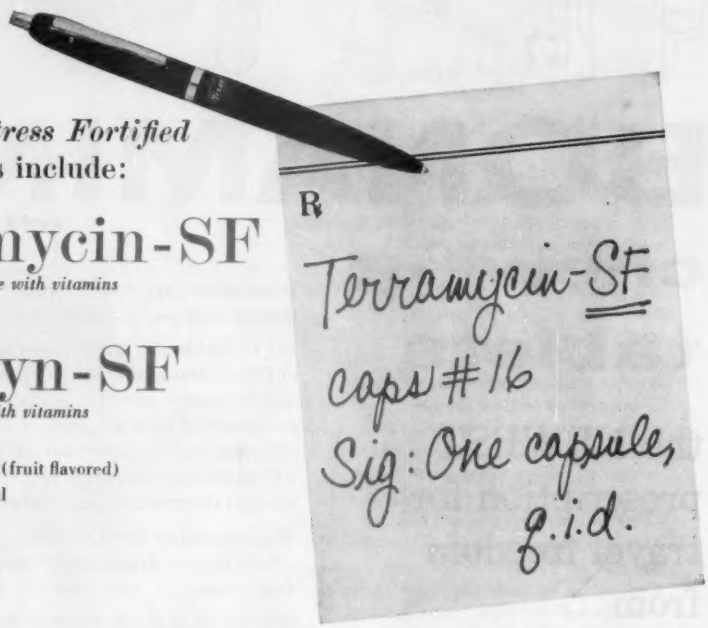

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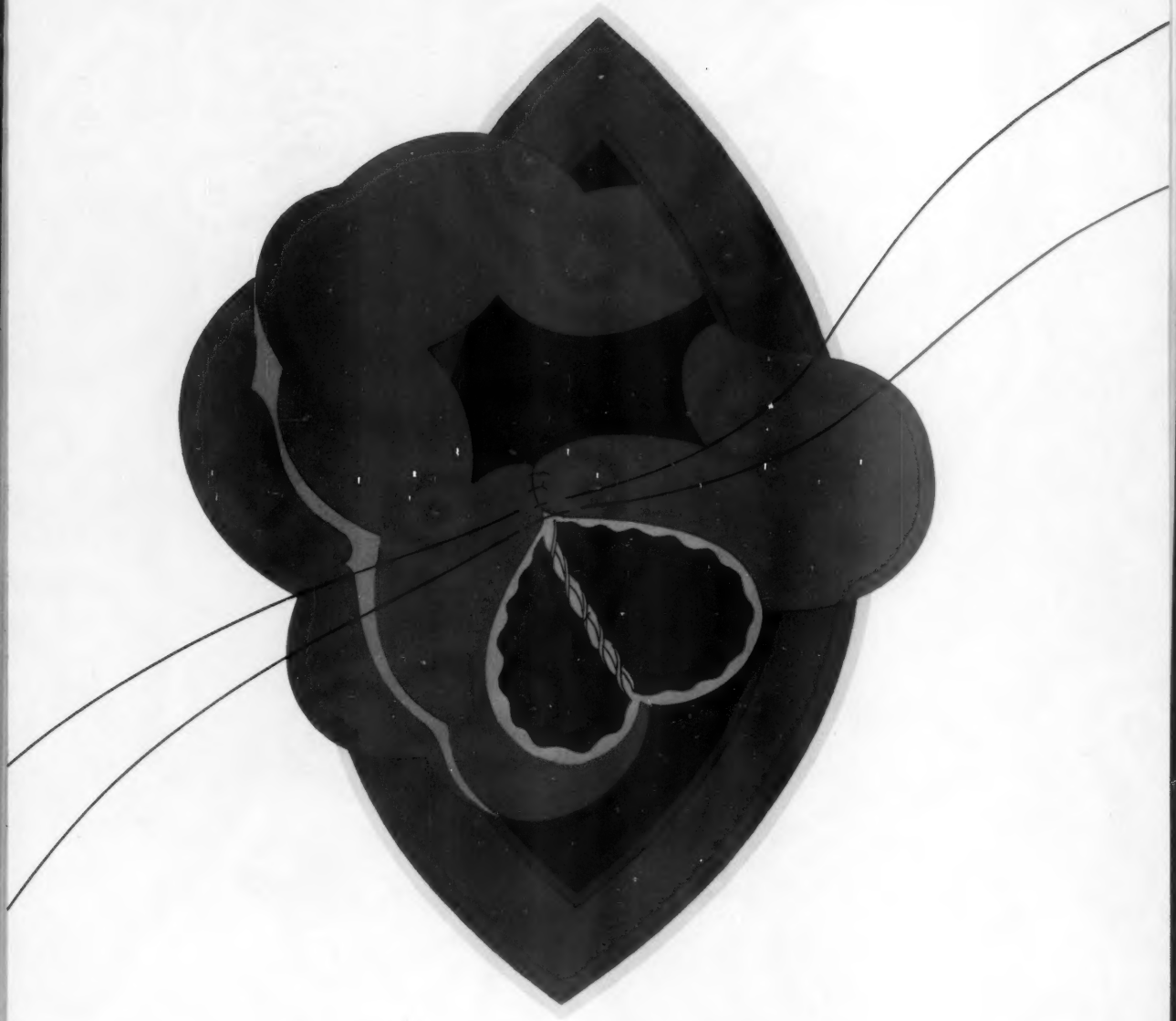

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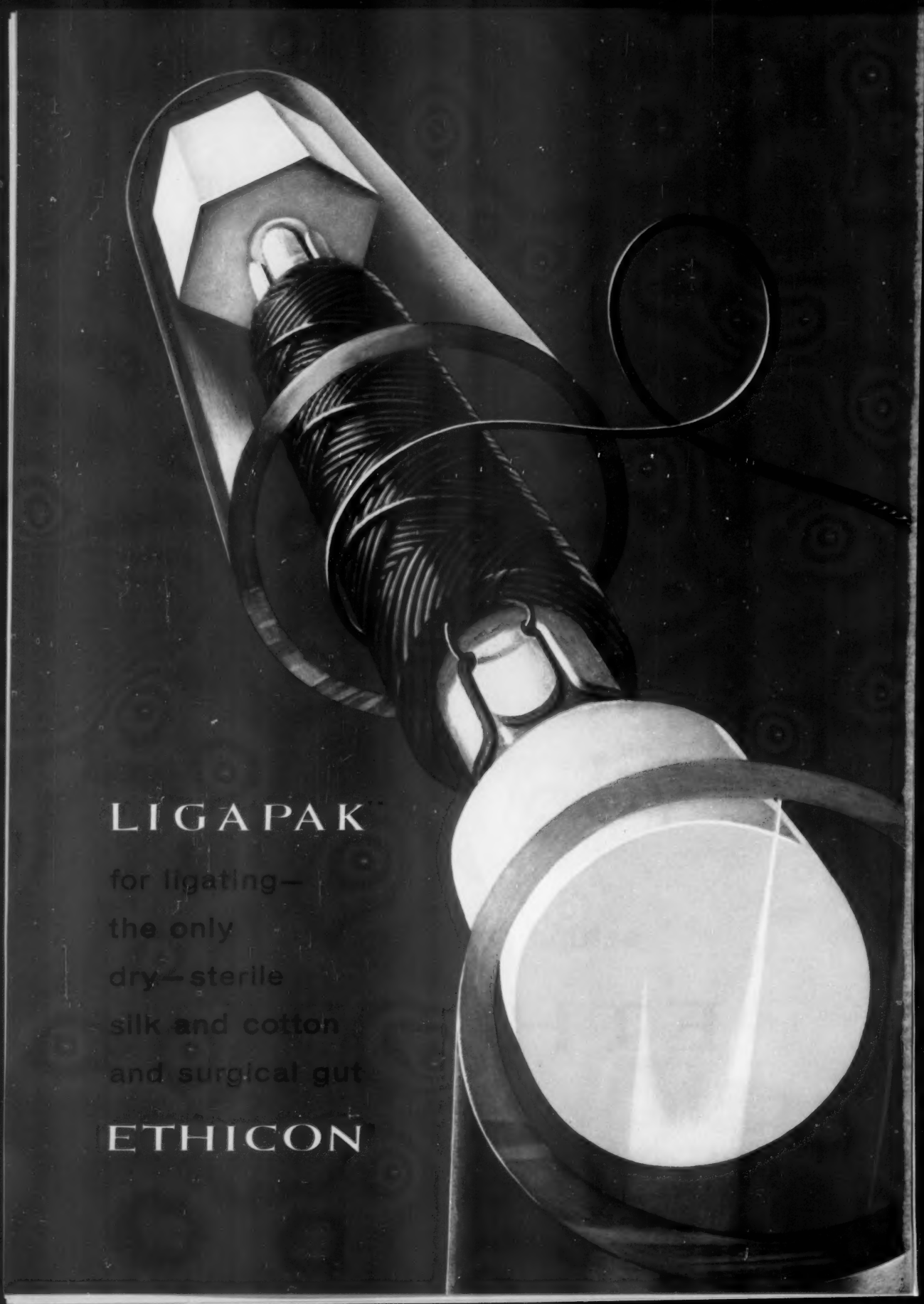
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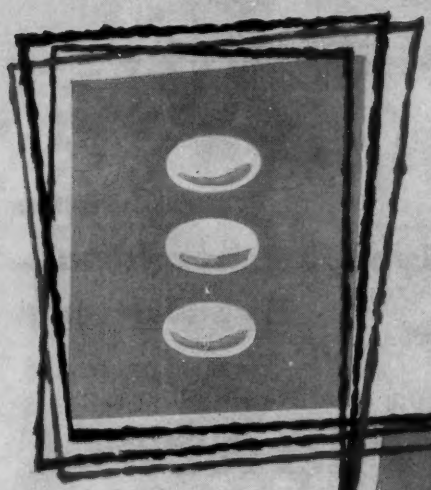

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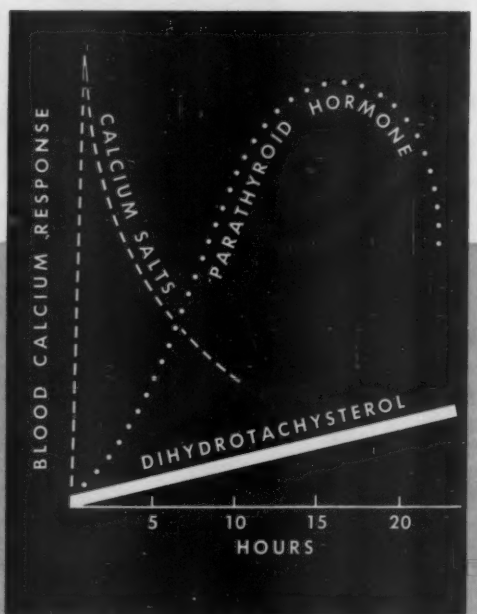

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Volume 252 JUNE 2, 1955 Number 22

SURGICAL MANAGEMENT OF MASSIVE ACUTE UPPER GASTROINTESTINAL HEMORRHAGE*

CLAUDE E. WELCH, M.D.,† ARTHUR W. ALLEN, M.D.,‡ AND GORDON A. DONALDSON, M.D.§

BOSTON, MASSACHUSETTS

SHORTLY after World War II the therapy of acute massive upper gastrointestinal hemorrhage changed radically throughout this country. Repeated generous whole-blood transfusions and early feeding replaced the method of infrequent transfusions and starvation. In a number of hospitals, coupled with these innovations, a vigorous surgical attack was carried out on many patients.

In the Massachusetts General Hospital the management of these cases has evolved into the following pattern. On the ward services most patients with other than trivial hemorrhage are admitted to the Surgical Service, where they remain either until surgery is carried out or until a few days have passed without recurrence of bleeding. Thereafter, as on the private services, very close co-operation is maintained throughout the patient's stay by both surgeon and physician. Patients with severe bleeding are given a chance to see whether or not they will stop spontaneously. In many cases persistent or recurrent hemorrhages will force operation as an emergency. In others an operation is done a few days later, and, in some, surgery is carried out in an interval period several weeks after the hemorrhage. The indications for each of these considerations are discussed below.

Formerly, patients with massive hemorrhage had been admitted to the Medical Service, and relatively few were operated on soon after admission. Thus, during the period 1938 to 1947,[1] 45 patients were operated on within forty-eight hours of the onset of bleeding from ulcer, and 44 per cent of the total had a definitive surgical procedure at some time to control the hemorrhage or to prevent recurrence. From 1948 to 1953, 100 patients had emergency operations for the control of bleeding from ulcer, and the rate of those with massive hemorrhage who finally had surgical therapy rose to 69 per cent. Sufficient time has elapsed to allow an evaluation of the effectiveness of this new trend in the management of hemorrhage.

General Considerations

The severity of the hemorrhage should be defined as accurately as possible since essentially all the mortality occurs with the severe grades. Stewart, Sanderson and Wiles[2] made an outstanding contribution when they defined massive hemorrhage from ulcer in terms of loss of circulating red-cell mass. By this definition any patient whose total circulating red-cell mass was less than 60 per cent of normal had had a massive hemorrhage. This precise statement may be contrasted with various clinical definitions of the same term that have been used. For example, a massive hemorrhage has been described as "one that endangers life" — a statement that defies objective interpretation.

We wish that we had data similar to those of Stewart and his associates to compare accurately with their material. However, since blood-volume studies have not been available, we have selected a less exact method. This is the same as that used in a previous report, in which massive hemorrhage is defined as one that has caused a fall in hemoglobin to 7 gm. per 100 cc. or below, or has required five or more transfusions during the period of hospitalization. As a matter of fact the average amount of blood given to these patients by transfusion was 5500 cc. Moderately severe hemorrhages have produced a hemoglobin level of 7 to 10 gm. per 100 cc. and have required less than five transfusions. Minor hemorrhages include all others and will not be considered further. By these criteria, 269 massive and 146 moderately severe hemorrhages from ulcer were observed at the Massachusetts General Hospital from 1948 to 1953.

Though a variety of lesions will produce massive hemorrhage manifested as hematemesis or by tarry stools, ulcer is by far the most important from the point of view of the surgeon. Except when specifically stated, this discussion is therefore limited to the control of bleeding from ulcer. The approximate frequency of upper gastrointestinal bleeding from all

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sources is shown in Figure 1. It may be observed that the highest lesion demonstrating hematemesis or tarry stools was a bleeding ulcer in the midesophageal region, and the lowest a carcinoid in the terminal ileum. About 50 per cent of the massive hemorrhages were due to gastric or duodenal ulcer.

Indications for Operation

Briefly, the indications for emergency operations for massive hemorrhage from any source in the upper gastrointestinal tract have been persistent bleeding at a

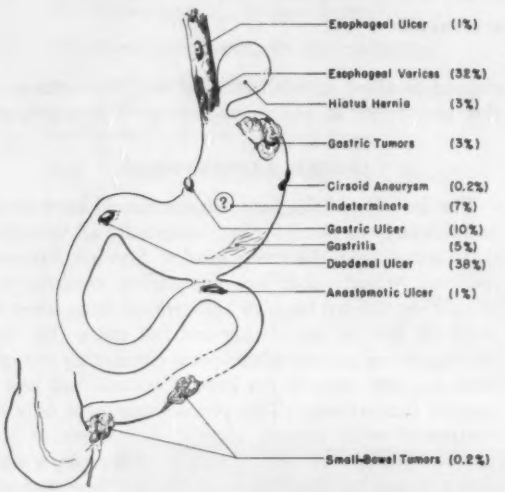

Figure 1. *Causes of Massive Upper Gastrointestinal Hemorrhage (1948-1953).*

rapid rate or recurrence of active bleeding after a free interval, in a patient with a positive or presumptive diagnosis of ulcer or tumor. It follows that early x-ray examination is frequently required to establish the diagnosis. Fortunately, when the hemorrhage originates from a hiatus hernia or gastritis, the bleeding stops spontaneously much more frequently than with ulcer. Therefore, when the presumptive cause of the blood loss is either hernia or gastritis, it is justifiable to withhold surgery for a longer period in the hope that an operation can be avoided if the diagnosis is gastritis or done as an interval procedure if it is hernia.

Several other factors are important in the decision regarding the time of the operation. Older patients, if other conditions do not preclude it and the patient is not moribund from some other disease, should be operated on as soon as the diagnosis of massive hemorrhage from ulcer is made, although this was not done consistently. This relation of age to ulcer surgery and mortality is discussed fully below. Patients with gastric ulcers are more likely to die from hemorrhage than those with duodenal, and operation should not be delayed. If the supply of compatible blood is low, as it often is in these times of so-called plenty, operation should be done before the bank is exhausted. Every attempt should be made to perform the operation at an opportune time of day when personnel and instrument problems will be reduced to a minimum. It is obvious that surgical mortality can be kept at a low figure by refusal to operate on many poor-risk patients; that has not been our policy. We have believed that in general the poor-risk patients tolerate bleeding less well and that bleeding should be corrected as soon as possible. Such factors as concomitant cardiac disease and cerebral arteriosclerosis or renal disease, manifested by a high nonprotein nitrogen, have elevated the mortality, but, when a surgeon has been in charge and his advice accepted by the patient, operation has not been delayed because of these accompanying diseases when the other indications for surgery mentioned above are present.

It is our belief that every patient who has a single massive hemorrhage from ulcer should be operated on since previous follow-up study has shown recurrent bleeding months or years later in 25 per cent of such patients who recovered after medical therapy alone.[1] The significant problem, then, in such patients, is to decide the opportune time for such surgery.

Method of Therapy

A brief summary of the methods of operative therapy of these patients will indicate how they are treated at present. Usually, after the patient is admitted to the ward, the blood pressure is stabilized, and active bleeding ceases. This time is chosen for an emergency x-ray examination if the diagnosis is not clear from the history or physical examination. By means of Hampton's[8] nonpalpation technic, the majority of bleeding ulcers may be demonstrated (Fig. 2 and 3). Emergency esophagoscopy or gastroscopy is used occasionally but not routinely.

When an emergency operation is necessary, a Levin tube is passed, and transfusions started through one or two large-bore needles. Usually, three or four transfusions are given during the operation. A cuffed intratracheal tube is placed and inflated under topical anesthesia, and the operation continued under ether anesthesia.

The abdomen is opened through an adequate incision, and the site of bleeding determined as rapidly as possible. If the upper jejunum is full of blood, the bleeding point must be identified promptly by gastrotomy or duodenotomy, and the hemorrhage controlled by digital pressure if necessary. If the stomach is full of blood the clot must be evacuated by gastrotomy. Nearly always, by palpation or gastrotomy, the source of the hemorrhage can be determined. In the rare case in which none is found the entire small bowel must be examined with great care. If it too is normal we deem it wiser to proceed with a subtotal gastrectomy since the bleeding in these cases usually

arises from a gastritis; the gastric remnant and open duodenum must be examined with great care.

The operation to be carried out is a distal partial gastrectomy, about 75 per cent of the stomach being removed. Individual ligation of the vessels without resection was discarded many years ago as inadequate. This gastrectomy should preferably include removal of the ulcer. At times, however, the surgeon may decide that it is safer to divide the duodenum proximal to the ulcer. If this resection for exclusion is practiced, any postoperative hemorrhage may be assumed to originate from the ulcer bed and will require secondary operation. Double jejunostomy tubes are usually inserted, and the abdomen is closed with great care. Antibiotic therapy is started before operation and is continued for five days afterward.

FIGURE 2. *Demonstrations of a Duodenal Ulcer by Hampton's Technic. The ulcer is shown in the spot film just beyond the pylorus. The patient was operated on for acute massive hemorrhage a few hours later.*

The over-all mortality of approximately 17 per cent after surgery may be broken down into one of 25 per cent after 100 emergency operations, with 25 deaths, and one of 7 per cent after 86 elective operations, with 6 deaths (Table 1). It is apparent that this operative mortality is surprisingly high. To understand the causes, it is first necessary to analyze the factors causing the deaths that followed emergency operations.

The pulmonary complications are the most important (Table 2). They cannot be eliminated by the routine use of antibiotics. It is possible that some of them that are due to vomiting of gastric contents under anesthesia could be reduced by the use of local rather than ether or cyclopropane anesthesia. Yet it has seemed impossible to us to perform an adequate technical procedure on these patients, most of whom seem to be obese, without general anesthesia. Extreme care must be taken to avoid aspiration during the operation, for it is easy for a partially anesthetized patient to vomit a stomach full of clot, to aspirate it and literally to drown in his own blood. The Levin tube is always passed before operation. Before the anesthetic is given the larynx is cocainized, and a cuffed intratracheal tube is inserted. Thereafter, any vomiting of blood or clot can be controlled com-

FIGURE 3. *Demonstration of a Gastric Ulcer and Hiatus Hernia by Hampton's Technic.*
The gastric ulcer was constant in all films. At operation, carried out immediately, this eighty-two-year-old man was found to be bleeding actively from the ulcer.

pletely by the anesthetist. The most common type of pulmonary complication is aspiration pneumonia. That aspiration is an important common cause of postoperative pulmonary complications has been known for many years, but has not been appreciated generally until recently.

Culver, Makel and Beecher[4] demonstrated how easily gastric contents are regurgitated and aspirated during anesthesia. The same complication is frequent in the early postoperative days and has caused deaths as long as two weeks after operation. The two factors necessary to produce it are a full stomach, or one with an incompetent cardiac sphincter, and depression of the cough reflex. The first of these may be counteracted easily if the stomach is kept empty during the early postoperative period. One can show the necessity for this precaution by giving a drink of barium to a patient who has a minor degree of stomal obstruction or who has had a long-standing pyloric obstruction before operation. Strong regurgitant waves can often be demonstrated in the esophagus. It is no wonder that aspiration occurs under the circumstances, particularly when the cough reflex has been dulled by oversedation.

Decompression of the stomach can be obtained by the Levin tube. We have felt it advantageous to use a catheter introduced in a retrograde fashion through the efferent jejunostomy loop into the stomach, as first described by Allen and Donaldson.[5] This will allow much better clearing of the respiratory tree than can occur when the pharynx is continuously irritated by the Levin tube. Furthermore, this catheter can be tolerated much better and longer than a nasal tube. It is especially important to use this technic in elderly, depleted and very ill patients, who are well known candidates for postoperative pulmonary complications or stomal obstructions.

Table 1. *Mortality by Age Groups in Massive Hemorrhage from Ulcer.*

Age yr.	Medical Therapy		Emergency Operations		Elective Operations		Total Operations		Total Medical and Surgical		
	No. of cases	No. of deaths	No. of cases	No. of deaths	No. of cases	No. of deaths	No. of cases	No. of deaths	No. of cases	No. of deaths	Mortality %
0-9	1	1	0	0	1	0	1	0	2	1	50
10-19	2	0	2	0	0	0	2	0	4	0	0
20-29	4	0	1	0	2	1	3	1	7	1	13
30-39	5	0	4	0	4	0	8	0	13	0	0
40-49	12	1	12	2	24	0	36	2	48	3	6
50-59	25	6	20	2	33	2	53	4	78	10	13
60-69	20	3	34	13	15	1	49	14	69	17	25
70-79	9	2	24	7	6	1	30	8	39	10	26
80-89	4	1	3	1	1	1	4	2	8	3	38
90+	1	0	0	0	0	0	0	0	1	0	0
Totals	83	14	100	25	86	6	186	31	269	45	
Average											17

Table 2. *Causes of Postoperative Deaths (1948-1953).*

Cause	No. of Cases
Pulmonary complications (aspiration 6, pneumonia 3, emboli 2)	11
Hemorrhage (continued shock 2, uncontrolled bleeding 3)	5
Miscellaneous technical errors (sepsis 2, pancreatitis 2, perforated duodenal stump 1)	5
Miscellaneous complications (cardiovascular anomaly 1, arterial thrombosis 2)	3
Indeterminate	1

Pulmonary emboli constitute another important cause of postoperative morbidity and mortality. At present we believe that the most important features of treatment are prophylactic. Early operations reduce the period of hypotension in which thrombosis is most apt to occur. Routine use of elastic stockings has been employed since the convincing evidence of Wilkins and his associates[6] appeared. Postoperative leg exercise and early ambulation are used, and tight compressive abdominal binders avoided. Prophylactic anticoagulants have been given to many patients, but prothrombin times are rarely allowed to fall below 20 per cent of normal. If thrombophlebitis of the legs develops or a pulmonary infarct occurs, interruption of the femoral veins is carried out.

Continued shock after operation had led to death in 2 cases. Here, several corollary statements may be made. These deaths can best be avoided by an operation carried out just as soon as the indications are clearly established. Equally important is the performance of an expeditious operation. Procedures that required total gastrectomy in 2 cases of high gastric ulcer and transthoracic approaches in 3 cases of esophageal ulcer were all fatal, almost surely because of the difficult, protracted operations.

Closely related is technical inability to control hemorrhage. Although continued bleeding after op-

eration occurs from many causes, it is encountered most frequently when a duodenal ulcer is excluded rather than resected. It is obvious that actual resection of all bleeding ulcers is not only difficult but very hazardous.[7] Our policy with such problems is to exclude the ulcer only when resection would be dangerous and active bleeding from it cannot be demonstrated at the time of the operation. If bleeding recurs in the early postoperative period after ulcer has been excluded, as in 5 cases in this series, the ulcer should be resected, and the bleeding vessels actively controlled. In 3 cases in which re-exploration was done the patients survived, whereas in 2 in which it was not done the patients died.

Complications referable to the duodenal stump include perforation ascribable to insecure closure, which occurred only once, and pancreatitis. Although pancreatitis cannot always be avoided, its frequency varies directly with the amount of trauma inflicted on the pancreas. We believe that by far the most effective way to avoid these complications is by the acceptance of a catheter duodenostomy when a deep difficult dissection would be necessary to close the stump.

Some postoperative deaths have been due to a summation of a number of minor complications, none fatal in themselves. Wound dehiscence, localized sepsis in the subphrenic space and stomal obstruction with continued malnutrition may be mentioned as examples. In others a coronary or cerebral thrombosis may be initiated by a prolonged period of hypotension.

A factor difficult to assess, but undoubtedly important in many of these cases, is that of electrolyte imbalance. Particularly when stomal obstruction develops in elderly, depleted patients continued aspiration of gastric contents and replacement therapy, which has consisted of intravenous dextrose in saline solution, produces a hypochloremic hypokaliemic alkalosis. Death occurs later, and autopsy indicates some anatomic factor such as focal peritonitis that would probably have healed spontaneously if the patient had been in good electrolyte and nutritional balance. Adequate replacement of potassium is the most important feature in the prevention of this syndrome.

It must not be assumed that these principles of therapy were applied regularly in all cases after surgery for massive hemorrhage. However, during the years 1946 to 1953, we personally operated on 55 patients with massive hemorrhage from ulcer in which these principles were followed. Except for those operated on in 1946 and 1947, all are included in the total group of 269 mentioned above. They form a highly selected subgroup since they nearly all were private patients, unlike many of the ward patients. Extreme obesity, alcoholism and malnutrition were relatively uncommon although they are frequently encountered in ward patients. Private patients probably appreciate sooner the fact that they are bleeding, report earlier for treatment and are more cooperative in accepting advice. Most important is the fact that the decision to operate on a private patient can be translated immediately into action since, at most, a surgeon and a single physician are all that are required to reach an agreement. On the wards, on the other hand, the decisions are slower merely because more persons are involved. Finally, postoperative nursing care is bound to be more satisfactory on the private floors, where the personnel problem is not so acute.

In this subgroup of 55 patients there were 2 deaths. Both patients had had previous perforations, one with a large subhepatic abscess and the other with an acute general peritonitis. Both had two-stage gastrectomies performed. One died of a bleeding anastomotic ulcer, approximately two months after that time; the other died a week after operation from a perforated gall bladder. This relatively low mortality makes us believe that the opportunities that surgery can offer have not yet been fully exploited, and that a very important reduction in postoperative mortality can be attained by attention to particular details of operative care.

Discussion

It is necessary to compare the results of surgical therapy over an extended period to judge whether or not this modern method of management of bleeding ulcers is of value. From 1923 to 1932, Allen and Benedict[8,9] found that 165 patients with massive hemorrhage from duodenal or gastric ulcer were treated at the Massachusetts General Hospital, with an over-all mortality of 13 per cent. Only 8 of them had emergency operations for the control of the hemorrhage, and all died. In the decade 1938 to 1947,[1] 253 patients with massive hemorrhage from duodenal or gastric ulcer were seen, with an over-all mortality of 13 per cent; emergency operations were performed in 45 cases, with a mortality of 22 per cent. In the present series there were 269 patients with such hemorrhages, and the mortality was 17 per cent; 186 were operated on, 100 as emergency procedures, with a mortality of 25 per cent, and 86 as interval operations, with a mortality of 7 per cent. In the 83 patients treated medically the mortality was 17 per cent.

The obvious conclusion is that the over-all death rate from hemorrhage from ulcer has not diminished, but has increased slightly despite much wider application of surgery. What is the significance of this finding? Are we on the wrong track completely? Should early surgery be abandoned on the assumption that more patients are dying from operations who might recover if they were treated conservatively than are saved by these operations? We are certain that this assumption is not correct but that other factors are important.

In the first place it may be stated that this is a group of patients with very severe hemorrhage. For example, the average amount of blood given to each patient who had an emergency operation was 5500 cc. This is more than had been given previously and may indicate a more severe type of hemorrhage. In the second place surgical frontiers have broadened so that in this series, for the first time, esophageal ulcers with massive hemorrhage have been considered amenable to emergency therapy. A few lives have been saved, but the mortality has been very high in this particular group. The third and most important

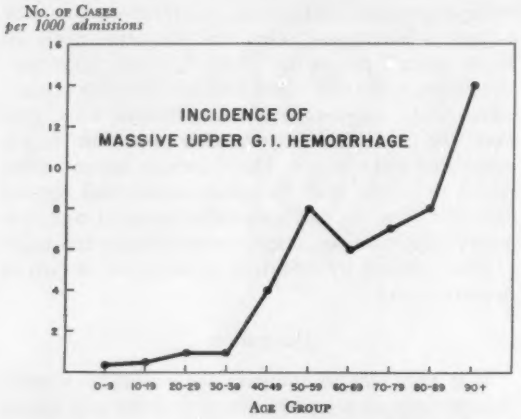

FIGURE 4. *Frequency of Massive Upper Gastrointestinal Hemorrhage by Age Group (Ulcer Patients Only).*

reason for the rising death rate is the changing character of the ulcer population seen in this hospital.

This requires a discussion of the relation of the age of the patient and his reaction to hemorrhage. It certainly must be admitted that age is often a poor milestone by which one can measure senescence and decay, but it serves in a rough way, and we believe that the following statements are justified.

In the first place massive hemorrhage from the upper gastrointestinal tract, and particularly that from ulcer, is much more frequent in the latter decades of life. This is not generally appreciated because many bleeding ulcers are seen in middle life. However, when one considers the proportion of patients admitted to the hospital in various age groups, it will be seen that massively bleeding ulcer becomes more common with the advancing years. Thus, 4 out of every 1000 patients admitted to the hospital between the ages of forty and forty-nine have an ulcer with massive hemorrhage, rising to 8 for 1000 patients admitted between the ages of fifty and fifty-nine, at which time a plateau is reached that continues through the ninth decade. Too few patients appear in this last decade for the high figures shown to be significant.

This means, of course, that as the average age of the hospital population increases, the number of bleeding ulcers will increase. This can be shown by many figures, but one will suffice (Fig. 4). At present, massive hemorrhage from duodenal ulcer is encountered fifteen times as frequently in patients over seventy years of age as it was in the decade of 1922 to 1932. It is also of interest that patients under forty years of age with massive hemorrhage from ulcer are much less common in this hospital than they were before, probably because many of these age groups are now treated in Army or Veterans Administration hospitals. Furthermore, the average age of patients admitted to this hospital was 36½ years in 1930 and 44½ years in 1951.

Secondly, mortality from massive hemorrhage increases with age. This fact is never disputed, and it is a reflection of the fact, which Ingelfinger and Sanchez[10] have pointed out, that all illnesses are tolerated more poorly in the aged. Our figures in this series (Fig. 5) show a steadily rising mortality with age.

It follows from these statements that any comparison of mortality rates from bleeding ulcer, treated either by medicine or surgery, must take into account the increasing age of the patient population. When this is done (Table 3), with a comparison of all patients treated by medical or surgical means, it is seen that there has been a fall in mortality from that noted

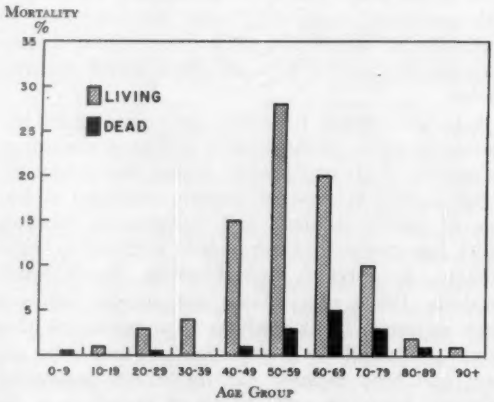

FIGURE 5. *Mortality from Massive Upper Gastrointestinal Hemorrhage by Age Group (Ulcer Patients Only).*

in 1923 to 1932 as time has gone on, in each group over fifty years of age. When the present series is compared with the intermediate one (1938 to 1947) there has been but little change except for a slight decrease in mortality in the sixth decade and a slight rise in the seventh. At present the mortality of surgical therapy for massive hemorrhage from ulcer is 6 per cent below fifty, 8 per cent fifty to fifty-nine, 29 per cent sixty to sixty-nine and 29 per cent over seventy years of age.

This discussion does leave unanswered the basic question, Would these patients do better on a program of early surgery or on conservative therapy that

includes adequate blood replacement? Some light can be shed on this question when one considers the behavior of a small but critical group, patients eighty years of age or older who enter with massive hemorrhage from any cause, many of whom had protracted medical treatment solely because of their age.

There were 17 such patients who entered the hospital with massive hemorrhage from all causes. The over-all mortality was 35 per cent. Medical therapy alone was carried out in 14. It was successful in 6, but in 3 no cause of hemorrhage was ever identified by x-ray study. Of the 11 patients with demonstrated lesions, medical therapy failed in 8 (73 per cent) since all the 8 had further hemorrhage. These secondary hemorrhages led to long-delayed surgery in 3 cases and to death in 4 other cases without operative intervention. The final patient lived and survived a second massive hemorrhage a few months later.

Three patients, as just noted, had medical therapy followed by late surgery. The failure rate, again, was high since there was only 1 survival.

Three others had early surgical therapy carried out within twenty-four hours of admission, and all survived.

This small group of cases in the critical age group confirms the statement made independently by Finsterer and Allen many years ago that early operation is necessary for success in elderly patients.

Moderately Severe Hemorrhage

It may be of interest to indicate the fate of the patients with moderately severe hemorrhage from ulcer since many authors include such hemorrhages in their figures on the mortality of massive hemorrhage. Usually, such patients are treated conservatively in this hospital, and operation, if it is to be performed, is done at an elective time.

Seventy-five patients had medical therapy alone, of whom 2 died from causes unrelated to the hemorrhage. Sixty-nine patients had surgical therapy, and of these, 9 were done as an emergency procedure, with survival in all. There were 60 elective operations with 2 deaths, 1 due to a perforated duodenal stump and 1 to a perforated sigmoid from a barium fecalith.

The surgical mortality in this group, therefore, was 3 per cent, and the over-all mortality of moderately severe hemorrhage 3 per cent. If these patients were included in the statistics for massive hemorrhage, the mortality from severe hemorrhage from ulcer would be 12 per cent.

Massive Hemorrhage from Lesions Other Than Ulcer

Only brief mention is made of the lesions that required surgical therapy for massive hemorrhage from lesions other than ulcer. They must be considered since the surgeon may expect to find an ulcer at the time of operation but in its absence must consider other possibilities. However, operations for control of acute massive hemorrhage from esophageal varices are not discussed, since they have been reported elsewhere by Linton and Warren.[11]

Seventeen operations were carried out as emergencies for the control of hemorrhage due to lesions other than ulcer. They included gastritis, a variety of tumors, hiatus hernia and ruptured cirsoid aneurysm. There were 6 deaths in this group. Seventeen other patients were operated on at an elective time, with no deaths.

Summary and Conclusions

A comparison of death rates from massive hemorrhage from ulcer, treated either medically or surgically, or in combination, in the Massachusets General Hospital, shows a slight increase from the decade 1923-1932 to the present, with a rise in mortality from 13 to 17 per cent.

This increased mortality, despite many more emergency operations, is due chiefly to two factors: the increasing age of the hospital population, and technical factors that have led to death from various postoperative complications.

Any mortality study of massive hemorrhage must take into account the age distribution of patients treated. In this series the mortality of all patients treated by either medical or surgical means is 7 per cent under fifty, 13 per cent fifty to fifty-nine, 25 per cent sixty to sixty-nine and 29 per cent seventy years of age or over.

Elderly patients appeared to tolerate early surgery better than expectant treatment, as shown by the individual consideration of all patients over eighty years of age with massive hemorrhage from any source.

It is believed that a continued lowering in mortality will depend on methods outlined for the prevention of postoperative complications and earlier surgery on patients with massive hemorrhage who are over sixty years of age. The application of these principles to a consecutive series of 55 patients with hemorrhage from ulcer operated on personally by us resulted in 53 recoveries and 2 deaths.

Table 3. *Mortality in Massive Upper Gastrointestinal Hemorrhage from Ulcer (All Types of Therapy) by Age Group.*

Age Group	Mortality (1923-1932)	Mortality (1938-1947)	Mortality (1948-1953)
yr.	%	%	%
Under 40	4	3	8*
40-49	7	7	6
50-59	27	17	13
60-69	42	18	25
70 or over	50	29	29
All ages	13	13	17

*Figure not significant — not enough cases.

References

1. Welch, C. E. Treatment of acute, massive gastroduodenal hemorrhage. *J.A.M.A.* **141**:1113-1118, 1949.
2. Stewart, J. D., Sanderson, G. M., and Wiles, C. E., Jr. Blood replacement and gastric resection for massively bleeding peptic ulcer. *Ann. Surg.* **136**:742-751, 1952.
3. Hampton, A. O. Safe method for roentgen demonstration of bleeding duodenal ulcer. *Am. J. Roentgenol.* **38**:565-570, 1937.
4. Culver, G. A., Makel, H. P., and Beecher, H. K. Frequency of aspiration of gastric contents by lungs during anesthesia and surgery. *Ann. Surg.* **133**:289-292, 1951.
5. Allen, A. W., and Donaldson, G. A. Jejunostomy for decompression of postoperative stomach. *Surgery* **15**:565-568, 1944.
6. Wilkins, R. W., Mixter, G., Jr., Stanton, J. R., and Litter, J. Elastic stockings in prevention of pulmonary embolism: preliminary report. *New Eng. J. Med.* **246**:360-364, 1952.
7. Warren, R., and Lanman, T. H. Surgery in bleeding peptic ulcer: urgent operation and principle of exclusion. *Surg., Gynec. & Obst.* **87**:291-298, 1948.
8. Allen, A. W. Acute massive hemorrhage from upper gastrointestinal tract, with special reference to peptic ulcer. *Surgery* **2**: 713-731, 1937.
9. Allen, A. W., and Benedict, E. B. Acute massive hemorrhage from duodenal ulcer. *Ann. Surg.* **98**:736-749, 1933.
10. Ingelfinger, F. J., and Sanchez, G. C. Indications for surgery of upper gastrointestinal tract. *New Eng. J. Med.* **250**:445-452, 1954.
11. Linton, R. R., and Warren, R. Emergency treatment of massive bleeding from esophageal varices by transesophageal suture of these vessels at time of acute hemorrhage. *Surgery* **33**:243-255, 1953.

THE ATRIAL ARRHYTHMIAS*

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MANY common arrhythmias observed in both atria and ventricles are similar although the atrial types have a few important distinguishing features. Thus, so far as therapy is concerned, the atrial arrhythmias are less responsive to procaine amide than the ventricular ones. On the other hand, quinidine exerts a stronger action on the atria.[1]

In general, atrial tachycardias do not, if present without complications, endanger life. Atrial paralysis from the failure of impulse formation in the sinus node or a failure of conduction of the impulse from its point of origin is usually compensated immediately by the escape of the deeper centers. Only when these are damaged do dangers arise; this situation is rare, but in recent years it has become more frequent during anesthesia since excessive preanesthesia medication often brings about a condition in which all centers are depressed. Even if atrial fibrillation lasts for decades no untoward effect will be noted, provided the ventricular rate is kept slow.

The atria are under control of the vagus nerves, whereas in the mammalian heart vagal effects on the ventricles are rarely seen and, when present, are of minor importance. Recently, it has been shown for the first time that carotid-sinus pressure may have a slowing effect on an ectopic ventricular center.[2]

The vagal effects on the atrium are complex and obscure. Increased vagus tonus inhibits impulse formation in the sinus node as well as sinoatrial and atrioventricular conduction. However, there is no proof that vagal stimulation inhibits or slows the conduction from fiber to fiber within the atrium; no widening of the P waves is observed from vagal stimulation experimentally or during carotid-sinus pressure in man. On the contrary, in the dog, block of the intra-atrial conduction by pressure or cooling is immediately abolished when the vagus nerves in the neck are stimulated.[3,4] These paradoxical results may be explained on the basis of the experimental data of Burn and his collaborators.[5] These investigations suggest that acetylcholine is a local hormone necessary for impulse formation and conduction in the heart; cardiac standstill, elicited in various ways, may disappear when the concentration of acetylcholine is increased.

During atrial flutter elicited by topical application of aconitine, faradic stimulation of the vagus nerves paradoxically increases the existing atrial rate[6,7]; this finding has been confirmed.[8] It has been claimed that the type of the vagal effect, inhibitory or stimulatory, depends on the atrial rate, acceleration developing with high and inhibition with lower rates.[9] This statement has not been substantiated. Even when an atrial tachycardia with a stable rate is created by topical application of aconitine, faradic stimulation of the vagus nerve in the neck may within a few seconds cause both inhibition and acceleration.[10] It is not the rate but the finer, hitherto unknown, mechanism of impulse formation that seems responsible. It is clear that if one assumes a continuous stimulus, the rate will depend on the duration of the refractory phase; when vagal stimulation shortens the refractory phase the rate should increase. However, if impulses are formed rhythmically, shortening of the refractory phase (of the monophasic action current of the center) should also increase the rate.

Aconitine-induced atrial extrasystoles increase in number after vagal stimulation,[11] and vagal stimulation during atrial flutter may cause rates up to 3000 per minute.[12,13]

Clinically, an increase of the number of atrial extrasystoles has been seen occasionally as the result of carotid pressure. Pertinent in this connection is Figure 1. The tracings were obtained from a seventy-four-year-old woman who had a mild kyphoscoliosis and emphysema and who was hospitalized three times for attacks of paroxysmal atrial tachycardia and once for paroxysmal fibrillation. The attacks had occurred every two or three months for the past twenty years and were precipitated by emotional disturbances. This

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tracing shows the appearance of atrial fibrillation and flutter during carotid-sinus pressure in a patient with paroxysmal atrial tachycardia. This has not previously been observed in man. Carotid-sinus pressure has rarely been known to convert atrial flutter into auricular fibrillation[14] or to elicit these two arrhythmias,[15,16] but never to produce them in the presence of paroxysmal atrial tachycardia.

In contrast to the ventricles, where specific fibers able to form automatic rhythmic impulses are found

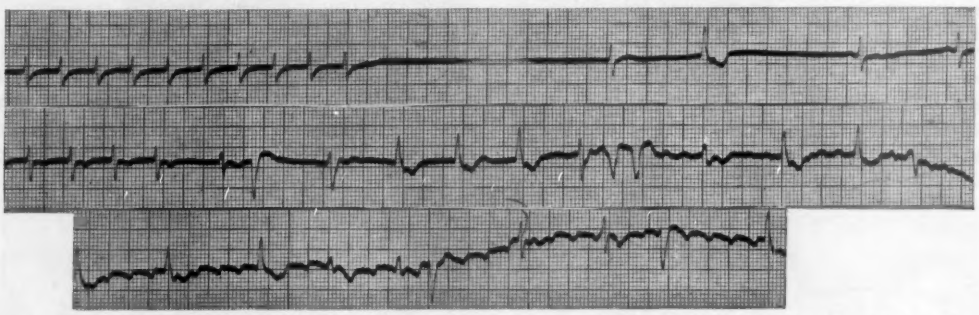

FIGURE 1. *Electrocardiograms in a Case of Paroxysmal Atrial Tachycardia That Was Stopped by Carotid-Sinus Pressure after an Intravenous Injection of Cedilanid.*

Pressure exerted before the injection was without effect. The pressure was carried out just when registration of the top tracing was interrupted. The second half of the tracing shows the first slow sinus beats and a ventricular ectopic beat while the carotid-sinus pressure was still being exerted. In the middle tracing, during another attack of paroxysmal tachycardia, carotid-sinus pressure abolishes the tachycardia, and abnormal ectopic beats as well as atrial fibrillation appear. The fibrillation, within a few seconds, is converted into flutter (bottom tracing).

in all parts, the atria possess such tissues only in the sinus node and the atrial portion of the atrioventricular node, these being the only areas where normal impulse formation takes place. When the heart of a dog in situ is sensitized by barium in such a way that no abnormal rhythm appears, warming of any part of the ventricular surface causes a ventricular tachycardia originating in the warmed area. Warming of different portions of the atria, at a distance from the sinus and atrioventricular nodes, has no effect on rate or rhythm.[11] On the other hand, with topical application of aconitine, an atrial tachycardia may be elicited from any area, even from the tips of the right or left atrium, where specific tissue is probably absent. How often atrial arrhythmias originate in common myocardial fibers is unknown, but certain observations show that the usual point of origin is in the nodes and their junctional fibers.

EXTRASYSTOLES

Atrial extrasystoles are said by many authors to be much less common than ventricular ones. They are not unusual, however, in patients with coronary sclerosis and do occur when coronary occlusion interrupts the blood supply to parts of the atrium. The extrasystoles are a rare consequence of digitalis therapy; this is in contrast to the frequent occurrence of atrial ectopic tachycardias and fibrillation from digitalis.

It is difficult to separate extrasystoles from an arrhythmia that, although most common in elderly patients, occurs at any age and is characterized by a continuously changing form of P waves, of the duration of the PR interval and of the rate. In my opinion this arrhythmia, usually called "shifting" or "wandering of the pacemaker," is often accompanied by atrial extrasystoles (Fig. 2). It demands the administration of quinidine since atrial fibrillation usually appears in a short time. In this disturbance ectopic automatic beats and forced beats — that is, extrasystoles elicited by the preceding complex — are simultaneously present.

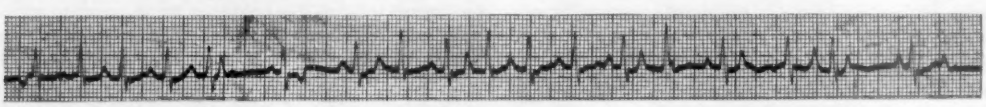

FIGURE 2. *Shifting of the Pacemaker with Continuously Changing Form of the P waves, the PR Interval and the Rate.*

Premature atrial contractions appear during atrioventricular block; Figure 3 shows a typical sample of this curious and common disturbance. These premature contractions are caused by reversed conduction of a ventricular automatic beat to the atria, stimulating them prematurely. The mechanism of retrograde conduction, often taking place in less than 0.20 second, in hearts in which the normal, orthograde conduction is absent, is a striking phenomenon for which no satisfactory explanation has been offered. Fascinating theories are available. The retrograde conduction occurs only when the ventricular complex appears in a certain relation to the preceding P wave — that is, in a certain phase of atrial diastole. Therefore, the presence of a supernormal phase of excitability has been assumed to be responsible. However, ventricular com-

plexes appearing in earlier phases of atrial diastole clearly cannot be conducted reversely because the atria are still refractory. The duration of this period, partly indicated by the presence of the Tp wave, may be longer than 0.50 second. On the other hand, ventricular beats occurring late in diastole are not conducted backward to the atria because the normal P wave appears in the meantime. This is the reason why only ventricular complexes appearing in a very limited phase of atrial diastole can show this phenomenon, without the supernormal phase as the cause.

Paroxysmal Tachycardias

This disturbance of the normal rhythm appears in countless variations and forms, many of which have been described by Gallavardin and his pupils.[17]

ular complexes. Too often the diagnosis of nodal (that is, atrioventricular nodal) tachycardia is then made without adequate justification. Actually, this form of tachycardia, like a paroxysmal tachycardia originating in the head of the sinus node, is rare. The centers best endowed with normal automatic impulse formation have little inclination to form heterogenetic impulses.[11]

If the P waves are invisible in a paroxysmal atrial tachycardia and a bundle-branch-block coexists or the ventricular complexes are aberrantly conducted, the impression of a ventricular tachycardia is created.

For unknown reasons atrial tachycardias and fibrillation are not rare in the Wolff–Parkinson–White syndrome. I favor the following explanation: an impulse that reaches the ventricles via the normal atrioventricular conduction system may be reversely con-

Figure 3. *Complete Atrioventricular Block (Lead 2).*

The large P waves are a common and unexplained finding in this condition. The fourth and seventh ventricular complexes are conducted back to the atria; deeply inverted, peaked P waves are visible between QRS and T. The retrograde atrial impulses do not disturb the intrinsic sinus rhythm since they arrive at the sinus node at a moment when it has just formed a normal impulse.

The separation of atrial paroxysmal tachycardias from atrial flutter is difficult and in some cases impossible. The often-repeated assertion that the atrial waves in paroxysmal tachycardias are separated by an isoelectric line whereas in flutter the string is in continuous motion, imitating a saw-tooth pattern, is not substantiated by many clinical and experimental tracings. Some authors suggest that there is no difference between these two disturbances, both of which have been repeatedly ascribed to a circus movement. On the contrary, aconitine experiments indicate that flutter and paroxysmal tachycardias are due to impulse formation in an ectopic abnormal center.[7,18] Nevertheless, both arrhythmias merit separation pending further data. Although vagal reflexes stop paroxysmal tachycardias, some clinical experience and much experimentation show that the atrial rate in flutter is increased by vagal stimulation or carotid-sinus pressure. Carotid-sinus pressure has never reestablished sinus rhythm in clinical atrial flutter. Flutter in patients with cardiac disease often precedes fibrillation whereas paroxysmal tachycardias rarely do. One can readily transform atrial flutter into fibrillation by the administration of digitalis, but this seldom succeeds in tachycardias. Digitalis abolishes the tachycardia or remains ineffective but does not usually cause fibrillation. A number of different compounds promptly help in paroxysmal tachycardias, but they are useless in flutter.

In atrial tachycardias the P waves are often invisible since they are hidden in the preceding ventric-

ducted to the atria by way of the abnormal path. If it reaches the atria early in diastole during the so-called vulnerable phase, it leads to rapid firing of impulses and not to a single depolarization. A similar mechanism may explain ventricular arrhythmias in this syndrome.

Recent attempts to attribute the pre-excitation syndrome to an acquired lesion — for instance, an irritable focus in the atrioventricular node or upper part of the interventricular septum — lack a substantial foundation. They are based mainly on the realization that mechanical stimulation of these areas in the dog and in man (during cardiac catheterization) leads to the appearance of abnormal ventricular beats preceded by normal P waves with a short PR interval. This is fortuitous, since automatic ectopic rhythms often have a rate that is the same or almost the same as that of the existing sinus rhythm.[11]

Atrial Flutter

The reasons why it is still considered necessary to separate flutter from paroxysmal tachycardia were mentioned above. Both arrhythmias have a common origin in one focus of rapid impulse formation. Even Lewis[12] did not consider a circus-movement mechanism in paroxysmal atrial tachycardia since the rates usually found in this disturbance are much too slow. If the size of the heart and the rate of the propagation of an impulse are taken into consideration a circus movement with rates of 180, as often seen in

paroxysmal tachycardia, is impossible. Since flutter can be created in any part of the atria by topical application of aconitine and can be stopped by cooling of this focus and caused to reappear when cooling is discontinued, the origin of flutter in one focus is proved.[6] On the other hand the responsibility of a circus movement for atrial flutter has not been demonstrated beyond doubt.

In recent years the circus-movement theory of flutter has received a new impetus from the experiments of Rosenblueth and Garcia-Ramos.[19] Persistent flutter is elicited with difficulty by faradic stimulation of the atria of a dog. The investigators found that clamping of a muscular bridge between the venae cavae superior and inferior, making it unable to conduct, permits one to elicit persistent flutter much more readily by faradization. They explain this by the fact that in the normal atrium the circus wave utilizes a short path around the vena cava superior before the crushing by the clamp and that therefore this path is readily stopped. The clamp forces the wave to utilize a more suitable path around the venae cavae superior and inferior. Therefore, a prolonged circus movement becomes possible.

Clamping does make the creation of prolonged flutter by faradization much easier. The explanation of the authors, however, is not the only one possible and is open to objections. Proof for the conduction of the circus wave in a circular path around the venae cavae is lacking. If flutter is created according to the manner described by them and a ligature is applied across this path wide enough to make a circus movement impossible, the rate and form of the P waves remains unchanged.[20] The more ready appearance of flutter after crushing can be explained by the fact that damaged muscle fibers in the crushed area are more easily transformed by faradization into centers for the formation of ectopic stimuli than normal tissue cells are. The focus of impulse formation may be situated anywhere in the atria if created by topical application of aconitine. Experimentally, flutter elicited by faradic stimulation can originate in the sinus node or the atrioventricular node. When the sinus node is eliminated, faradization or acetylcholine elicits flutter, which is promptly interrupted by cooling of the atrioventricular node. The P waves in this form of flutter are negative.

I have observed 1 case of clinical flutter with the origin of impulses changing from one center to the other. When the flutter disappeared the rhythm changed from sinus to atrioventricular rhythm in which the P waves exhibited the characteristic deep inversion in Leads 2 and 3. When flutter existed both positive and negative types of P waves or flutter waves were observed.

This patient was a sixty-five-year-old woman under treatment for coronary sclerosis (Fig. 4). The rates of the different foci were identical. During the transition from flutter with positive waves to one with negative P waves, isoelectric transitional P waves were observed (arrows in Fig. 4). These can be explained by fusion of positive and negative P waves. Those who still insist that flutter is due to a circus-movement mechanism may explain these changes in the form of the flutter waves by a change of the path of the circus waves. The fact that only combination forms of both types of P waves and no others were observed favors the interpretation advanced — namely, a change from one center to the other. Occasionally, both centers formed stimuli simultaneously and therefore combination P waves appeared; one part of the atria was activated by one center, and another part by the second. If a circus wave had altered its path, other forms of P waves should have been observed.

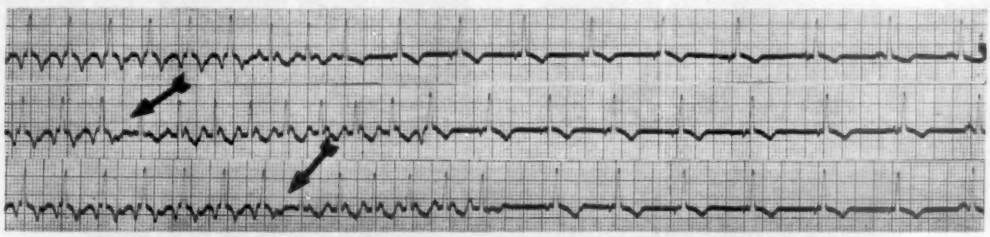

FIGURE 4. *Three Attacks of Atrial Flutter Changing into Atrioventricular and Sinus Rhythm (Lead 2). Note the almost isoelectric waves when an inverted P wave changes into a positive one (arrows).*

ATRIAL FIBRILLATION

In experimental fibrillation two mechanisms are possible. One focus may form impulses, but owing to the rapid rate, muscle cannot respond regularly. Therefore, these impulses spread irregularly over the atria, and some of them are blocked. The unifocal origin of fibrillation is demonstrated clearly since the fibrillation caused by topical application of aconitine on the dog's atrium can be transformed into flutter or sinus rhythm by focal cooling, and discontinuation of the cooling re-establishes the fibrillation within one or two seconds. This experiment can be repeated at will.[6,7]

The electrocardiogram of atrial fibrillation can also be seen when stimuli are rapidly formed in more than one center — for instance, in the sinus and the atrioventricular node (multifocal form).[18]

Fibrillation can also originate in the atrioventricu-

lar node alone (Fig. 5). In this experiment the sinus node had been clamped off, and fibrillation was induced by topical application of acetylcholine on the

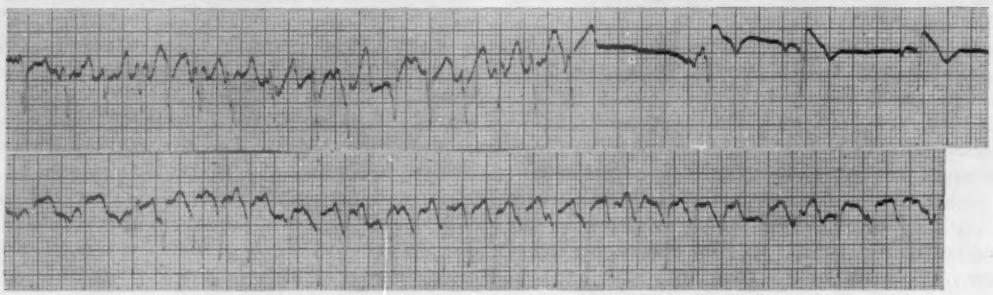

FIGURE 5. *Atrial Fibrillation from the Atrioventricular Node.*
The sinus node has been clamped off.
In the top tracing atrial fibrillation, which had followed topical application of acetylcholine to the right atrium of a dog, disappears immediately on cooling of the atrioventricular node. Slow atrioventricular rhythm appears. In the lower tracing, on withdrawal of the cooling thermode, atrioventricular rhythm changes again into fibrillation. Several repetitions of the experiment had the same results.

surface of the right atrium. Invariably, this fibrillation could be abolished by cooling of the atrioventricular node.

CONDUCTION DISTURBANCES

These appear in a great variety of forms, perhaps the most common being the widened P waves of mitral stenosis.

Atrial arrhythmias can result from atrioventricular

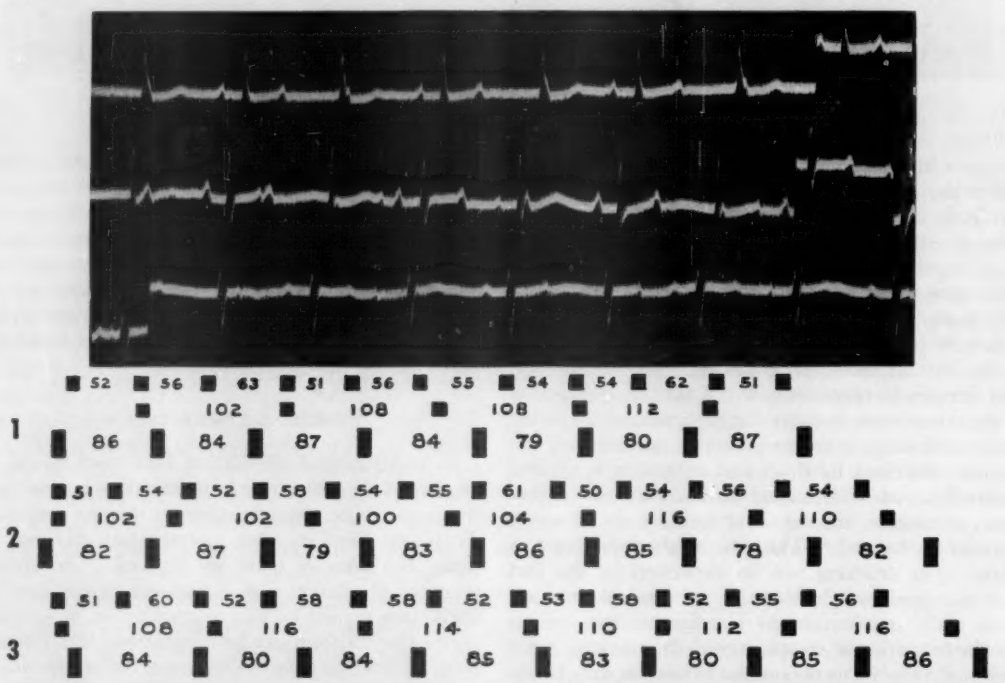

FIGURE 6. *Complete Block between Atria and Ventricles and between the Atria Themselves So That Simultaneously Three Independent Rhythms Exist.*
The graph gives the rate of these three rhythms.

It is probable that the commonest form of clinical fibrillation is the multicentric one, since rapid impulse formation in one center induces rapid firing of impulses in others.[18]

block, since the interatrial interval becomes prolonged in partial or complete block after a ventricular systole; this is due to the reflex increase of vagus tonus caused by stretching of the aortic wall as the blood is expelled by the contracting ventricle.

During atrioventricular rhythm or in ventricular extrasystoles, often an impulse that reaches the atria in a retrograde fashion may immediately return to the ventricle. Thus, one impulse, originating in an atrioventricular nodal or a ventricular center causes two ventricular and one atrial contraction (return extrasystole). This re-entry mechanism is not fully understood. During atrioventricular rhythm in the dog whenever the reversely conducted impulse reaches the atrium sufficiently late after the ventricular activation or whenever ventricular extrasystoles are conducted reversely to the atria, re-entry takes place. It seems, therefore, that, owing to a functional longitudinal dissociation, the atrioventricular system is always ready for re-entry.[21] Fibrotic septums, which were found in the conduction system, may facilitate such a mechanism.

Also of interest is the occasional existence of a block between the atria. This has been created experimentally,[22] and in few cases it has been seen in man. I have observed 4 cases. The blocks always occur in patients who are very ill; usually, they exhibit atrioventricular block, and death often follows in hours or days. Whenever an electrocardiogram points to the presence of this disturbance, one must be careful to rule out various artifacts that create the impression of rhythmically appearing P waves. Rhythmic contractions of skeletal muscles or of the diaphragm may be responsible.

Figure 6 was registered from a seventy-three-year-old woman one day before death from congestive cardiac failure due to coronary sclerosis. The ventricular rate was around 72. There was a complete atrioventricular block. Two types of rhythmically appearing P waves are present, one with an approximate rate of 54 and another form with a rate of 108 per minute.

Summary and Conclusions

Some controversial aspects of cardiac arrhythmias are discussed, and an attempt is made to explain the paradoxical effect of vagus stimulation on disturbed intra-atrial conduction.

The transformation of a paroxysmal atrial tachycardia into flutter and fibrillation by carotid-sinus pressure is demonstrated.

Reasons are given to justify the continuing distinction between atrial flutter and paroxysmal tachycardia in spite of recent experimental results. A case of auricular flutter that favors the assumption of a focus of rapid impulse formation is described.

The electrocardiogram typical of atrial fibrillation may be observed when one of several mechanisms is active: rapid impulse formation of one focus anywhere in the auricle created by aconitine; rapid focus in the atrioventricular node alone after abolishment of sinus-node activity with the aid of clamps; and activity of several centers. A case of interatrial block simultaneously with atrioventricular block is described.

References

1. DiPalma, J. R., and Mascatello, A. V. Analysis of actions of acetylcholine, atropine, epinephrine and quinidine on heart muscle of cat. *Am. J. Pharm.* **101**:243, 1951.
2. Galbey, M., Ladopulos, C. P., Roth, F. H., and Scherf, D. Changes in ventricular impulse formation during carotid pressure in man. *Circulation* **10**:735, 1954.
3. Drury, A. N. Further observations upon intra-auricular block produced by pressure or cooling. *Heart* **12**:143, 1925.
4. Lewis, T., and Drury, A. N. Effect of vagal stimulation on intra-auricular block produced by pressure or cooling. *Heart* **10**:179, 1923.
5. Burn, J. H., et al. Discussion: diagnosis of diabetes insipidus: action of nicotine on diuresis. *Proc. Roy. Soc. Med.* **43**:841-845, 1950.
6. Scherf, D., Romano, F. J., and Terranova, R. Experimental studies on auricular flutter and fibrillation. *Am. Heart J.* **36**:241, 1948.
7. Scherf, D., and Terranova, R. Mechanism of auricular flutter and fibrillation. *Am. J. Physiol.* **159**:137, 1949.
8. Prinzmetal, M., et al. Mechanism of auricular arrhythmias. *Circulation* **1**:241, 1950.
9. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E. *The Auricular Arrhythmias.* 387 pp. Springfield, Illinois: Thomas, 1952.
10. Scherf, D., Blumenfeld, S., Mueller, P., and Beinfield, W. R. On response of ectopic tachycardias to vagus stimulation. *Am. Heart J.* **45**:95, 1953.
11. Scherf, D., and Schott, A. *Extrasystoles and Allied Arrhythmias.* 531 pp. New York: Grune & Stratton, 1953.
12. Lewis, T. *The Mechanism and Graphic Registration of the Heart Beat.* Third edition. 529 pp. London: Shaw, 1925.
13. Winterberg, H. Über die Wirkung des Nervus Vagus und Accelerans auf das Flimmern des Herzens. *Arch. f. d. ges. exper. Physiol.* **117**:223, 1907.
14. Bellet, S. Diagnosis and treatment of cardiac arrhythmias. *M. Clin. North America* **30**:1307-1323, 1946.
15. Aalsmeer, W. C. On results and clinical significance of artificial stimulation of vagus in man. *Nederl. maandschr. v. geneesk.* **9**: 143 and 305, 1920.
16. Mandelstamm, M. Vegetative Herzreflexe und Flimmerarrhythmie. *Ztschr. f. klin. Med.* **118**:261, 1931.
17. Froment, R. *Les tachycardies paroxystiques ventriculaires.* 546 pp. Paris: Masson, 1932.
18. Scherf, D., Schaffer, A. I., and Blumenfeld, S. Mechanism of flutter and fibrillation. *Arch. Int. Med.* **91**:333, 1953.
19. Rosenblueth, A., and Garcia-Ramos, J. Influence of artificial obstacles on experimental auricular flutter. *Am. Heart J.* **33**:677, 1947.
20. Scherf, D., and Blumenfeld, S. Mechanism of auricular flutter caused by crushing and electrical stimulation. *Cardiologia* **24**:193, 1954.
21. Scherf, D. Return extrasystoles. *Proc. Soc. Exper. Biol. & Med.* **64**:228, 1947.
22. Scherf, D., and Siedeck, H. Über Block zwischen beiden Vorhöfen. *Ztschr. f. d. ges. exper. Med.* **127**:77, 1954.

CONVULSIVE THERAPY IN PSYCHOSES ACCOMPANYING PREGNANCY*

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PREGNANCY in psychotic patients is fairly common and ordinarily calls for no special precautions or adjunctive therapy other than those normally imposed and administered in pregnancy. From time to time, although infrequently, the use of various types of shock therapy may have to be considered in such cases. The psychiatric indications for these forms of treatment are well known, but the question of the advisability of their use arises in view of the coexisting pregnancy and the possibility that the pregnancy will not terminate in a full-term living child.

REVIEW OF THE LITERATURE

The literature reviewed to date contains but few articles, and references are made to a relatively small number of cases.

Goldstein et al.,[1] in 1941, described the treatment of a patient with thirteen convulsive seizures, produced by Metrazol, with delivery of a full-term viable child, and they stated that "the outcome of this case would seem to indicate that in pregnant women where an indication arises for the use of metrazol or insulin shock treatment, the treatment is justifiable on the basis of the apparent harmlessness of convulsive seizures due to these drugs and epilepsy."

In 1942 Thorpe[2] treated a patient with thirteen major convulsions during the fifth and sixth months of pregnancy.

Gralnick,[3] reporting in 1945, discussed the results of treatment in 2 patients, 1 receiving electroconvulsive shock and insulin-coma therapy, and the other insulin coma only. Both pregnancies terminated in the delivery of dead babies.

The author stated that "naturally one can draw no definite conclusions from the few cases so far treated, but it is possible that the insulin coma treatment rather than the electric, had something to do with the prenatal deaths — however, we may speculate that hypoglycemia causes some maldevelopment in the fetus which allowed it to live until the final month of gestation — but no further."

Polatin and Hoch,[4] also in 1945, described 2 patients, 1 three and a half and 1 seven months pregnant, both of whom were delivered of living full-term children after electroconvulsive shock.

Kalinowski and Hoch,[5] discussing insulin therapy in pregnant women, refer to the report of Gralnick, noting his conclusions, and state that "the absence of similar reports but the mentioning of two normal babies by McConell on the other hand, leaves the question of any connection open." They note, as others do, that electroconvulsive shock in pregnancy in epilepsy does not necessarily result in abortion or premature birth of the child due to the seizures.

Turner and Wright,[6] Moore[7] and Block[8] have reported single cases, and Sands[9] described 2 patients who were discovered to have been pregnant during the course of electroconvulsive treatment.

Kent[10] reported on 3 patients, of whom 1 received only electroconvulsive therapy, a second electroconvulsive therapy and insulin on an ambulatory basis and a third electroconvulsive and deep-insulin-coma therapy. Two viable children were produced. The patient given insulin on an ambulatory basis miscarried at four months. The author stated that "experience which has been recorded indicates that insulin treatment must be considered as an added risk to pregnancy and in some cases it would be debatable whether it is more of a risk than the symptoms caused by some types of mental illness."

Doan and Huston,[11] in 1948, added 7 cases to the 9 previously reported in the literature in which electroconvulsive therapy had been used during pregnancy. These 7 patients all received curare to soften the convulsions. One was treated in the first trimester, 4 in the second, and 2 in the third. In all, the delivery of normal infants was accomplished at term. On the basis of this experience and other reports in the literature, it seems that pregnancy is not in itself a contraindication to electroconvulsive therapy, and it also appears that curare may be used with safety.

There is agreement among the authors of obstetric textbooks[12,13] that pregnancy neither is affected by nor affects epilepsy and that in each patient the treatment must be individualized and special attention given to diet, elimination, rest and avoidance of worry and fatigue.

Consideration of the factors mentioned above leads one to conclude that when there are indications for the use of shock therapy in a woman who is pregnant, the treatment of choice should be electroconvulsive therapy.

CASE REPORTS

Since 1949, 86 psychotic pregnant women have been admitted to the Worcester State Hospital for the primary purpose of delivery. Of this number, 8 received electroconvulsive therapy during the period of gestation because of their disturbed mental state.

CASE 1. S.L., a 24-year-old married para ii, gravida iii, was admitted to the hospital with a diagnosis of schizophrenic

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reaction, hebephrenic type. She was overtalkative, overactive, agitated, noisy, unco-operative and silly, with impulsive behavior to the point of requiring residence on the ward for acutely disturbed patients. Pregnancy was suspected, but examination was impossible during the first 2 months. She received 18 electric-shock treatments, during which the diagnosis of pregnancy was confirmed. She was delivered of a full-term, normal, living male child 1 month after final treatment. Mother and child progressed normally during the puerperium.

CASE 2. V.K., a 37-year-old married para 0, gravida iii, was admitted to the hospital 14 weeks pregnant, with a diagnosis of psychotic depressive reaction. She showed pedal edema, and it was suspected that the fetus was dead. She was incoherent, confused and weeping, was fearful of losing her baby, was anxious, had difficulty sleeping and eating and thought that things were unreal. She was restless at night and frequently started physical conflicts with other patients (especially other psychotic pregnant women). The past history revealed 2 previous miscarriages. Because of overactivity, unco-operativeness, agitation, depression, anorexia and physical assaultiveness she was given electroconvulsive treatment. Between the 5th and 7th months she received 28 treatments, which produced 18 grand-mal seizures, with improvement. For an exacerbation of symptoms during the 8th month she was given 7 more treatments. Improvement followed, with no overt psychopathology. Two days after the last treatment, during the 34th week of pregnancy, she was delivered spontaneously of a living, well developed female infant weighing 2.1 kg. The puerperium was uneventful, and the child developed normally.

CASE 3. A.K., a 39-year-old married para i, gravida ii with a schizophrenic reaction, schizoaffective type, had received, before admission, 7 electroconvulsive treatments because of nervousness, depression, tearfulness and visible tremulousness. Examination of the abdomen revealed her to be 2 months pregnant. Seven months after the last treatment she was delivered of a full-term, living female child weighing 3 kg. The puerperium was uneventful, as was the infant's progress.

CASE 4. C.S., a 29-year-old married para 0, gravida i with a schizophrenic reaction, schizoaffective type, was admitted to the hospital in the 5th month of pregnancy. She was perplexed and anxious, showed guilt feelings, was deluded, hallucinated, with ideas of reference in her mental content. She was depressed, tearful, restless, confused and had feelings of unreality. She was unco-operative to nursing care and assaultive to other patients. She received 17 electroshock treatments, the last one being 7 days before delivery of a full-term living female weighing 3.5 kg. The puerperium and postnatal development were normal, and there was a remission of the tense, agitated unco-operative behavior.

CASE 5. J.E., a 35-year-old married para iii, gravida iv with a manic-depressive, depressed reaction, was agitated, noisy and extremely fearful. She thought that she was going to be killed, possibly as a form of punishment. She was unco-operative and resistive to nursing care. She received a course of 4 electric-shock treatments 2 weeks before delivery of a full-term, normal, viable female infant weighing 2.9 kg. Mother and infant were in good physical condition.

CASE 6. E.C., a 28-year-old married para ii, gravida iii with a paranoid type of schizophrenic reaction, showed symptoms of depression, preoccupation and perplexity and was deluded, hallucinated and in a state of turmoil. She received 20 electric-shock treatments during the 4th and 5th months of pregnancy and was delivered of a full-term female infant weighing 3.7 kg. 4 months after the last treatment. The postnatal and puerperal course was uneventful.

CASE 7. F.W., a 19-year-old unmarried para 0, gravida i, was admitted to the hospital 6 months pregnant with signs of a catatonic type of schizophrenic reaction. She wandered aimlessly about, was almost mute, mumbling incoherently, and was irrelevant and illogical. She reacted to hallucinations, and showed purposeless manneristic grimacing movements. Mental content was inaccessible, and she refused to eat. She received 7 electroconvulsive treatments up to the 8th month of pregnancy, with improvement of symptoms in that she talked freely and re-established her nutrition. Owing to a small platypelloid pelvis and a left shoulder anterior presentation, a cesarean section was performed at 8½ months of pregnancy, 14 days after the last shock treatment, resulting in delivery of a viable female child weighing 3.4 kg. The patient and her child did well after delivery.

CASE 8. M.P., a 20-year-old married para 0, gravida i, 4 months pregnant, was admitted to the hospital with a schizoaffective type of schizophrenic reaction. She was agitated and excited and was noisy to the point of requiring seclusion. She showed feelings of unreality, perplexity and denial of her pregnancy. She received 25 electric-shock treatments, with improvement of her psychotic symptoms during the 4th to 7th month. A full-term normal infant was delivered 2 months after the last treatment. The puerperium and postnatal conditions were uneventful.

DISCUSSION

The patients described above were all delivered of living, normal infants. The postnatal and puerperal states were without abnormal physical reactions. These 8 pregnant women were given electroconvulsive treatments without any adjunctive medication to soften the seizures. One patient received treatment during the second, 2 during the third, 3 during the fifth, 2 during the sixth, 3 during the seventh, 4 during the eighth, and 3 during the last month of gestation. Indications for active somatic therapy of the psychosis were present, and treatment was given primarily for symptomatic control of seriously disturbed behavior. The safety of the mother as well as the viability of the child might well be endangered by withholding shock treatment in such cases.

These cases, as well as those previously described in the literature, add weight to the belief that, when somatic treatment is indicated, electroconvulsive therapy is the method of choice. It appears to be safe, and it should not be withheld because of a coexistent pregnant state.

SUMMARY

The literature dealing with the shock treatment of women with evidence of both psychosis and pregnancy is reviewed.

In 8 patients electroconvulsive therapy alone was administered for control of the disturbed mental state. This somatic treatment was given in all trimesters of pregnancy, 2 patients receiving treatment during the final week of gestation, and 1 of these received her last treatment two days before delivery.

One patient in this series was delivered by cesarean section two weeks after treatment.

No untoward reaction as the result of this therapy was noted in either the patients or their offspring.

The observations in this study, together with those of others reported in the literature, seem to justify the use of electroconvulsive therapy in pregnant women who are severely disturbed mentally, and this form of therapy is believed to be safe in such cases.

References

1. Goldstein, H. H., Weinberg, J., and Sankstone, M. Shock therapy in psychoses complicating pregnancy. *Am. J. Psychiat.* **98**:201, 1941.
2. Thorpe, F. T. Shock treatment in psychoses complicating pregnancy. *Brit. M. J.* **2**:281, 1942.
3. Gralnick, A. Shock therapy in psychoses complicated by pregnancy. *Am. J. Psychiat.* **102**:780-782, 1946.
4. Polatin, P., and Hoch, P. Electroshock therapy in pregnant mental patients. *New York State J. Med.* **45**:1562-1565, 1945.
5. Kalinowsky, L. B., and Hoch, P. *Shock Treatments, Psychosurgery and Other Somatic Treatment in Psychiatry.* Second edition. 396 pp. New York: Grune & Stratton, 1952.
6. Turner, C. C., and Wright, L. D. Shock therapy in psychoses during pregnancy: report of case. *Am. J. Psychiat.* **103**:834-836, 1947.
7. Moore, M. T. Electrocerebral shock therapy: reconsideration of former contradictions. *Arch. Neurol. & Psychiat.* **57**:693-711, 1947.
8. Block, S. EST during pregnancy. *Am. J. Psychiat.* **104**:579, 1948.
9. Sands, D. E. Electroconvulsion therapy in 301 patients in general hospital. *Brit. M. J.* **2**:289-293, 1946.
10. Kent, E. M. Shock therapy during pregnancy. *Psychiatric Quart.* **21**:102-106, 1947.
11. Doan, D. I., and Huston, P. E. Electric shock during pregnancy: report of seven cases. *Psychiatric Quart.* **22**:413-416, 1948.
12. Titus, P. *Management of Obstetrical Difficulties.* Third edition. 1000 pp. St. Louis: Mosby, 1945. P. 217.
13. Beck, A. C. *Obstetrical Practice.* Third edition. 949 pp. Baltimore: Williams & Wilkins, 1942. P. 591.

SPECIAL ARTICLE

HISTORICAL BACKGROUND OF THE USE OF RADIOACTIVE IODINE IN MEDICINE*

J. H. Means, M.D.†

BOSTON

THE expansion of research on the thyroid gland that the past eighteen years have witnessed resulted from the meeting of two quite distinct lines of inquiry and discovery. The more ancient of these is that which through the centuries has identified the element iodine ever more closely with the thyroid gland, and the other, man's discovery that certain elements give off, or can be caused to give off, certain types of radiation. When these lines met, a new era opened in the progress of the understanding of the physiology and biochemistry of the thyroid gland and its diseases.

The thyroid-iodine relation can be traced back to antiquity. The ancients treated goiter with burnt sponge and seaweed, both of which contain iodine. Coindet,[1] in 1820, treated goiter with iodine and described in monographic form its beneficial effect. In 1896 Baumann[2] discovered that the thyroid gland contains iodine as an essential ingredient, and Marine,[3] in 1907, showed that iodine is necessary to normal thyroid function; four years later Oswald[4] found diiodotyrosine in the thyroid gland, and in 1915 Kendall[5] discovered thyroxine. Kendall, indeed, not only isolated thyroxine from the thyroid gland but purified it to crystalline form, and showed that this pure crystalline substance, containing by weight 60 per cent of iodine, relieved the clinical state of complete athyreosis as effectively as whole thyroid substance; thyroxine, as he called it, was presumed actually to be the hormone of the thyroid gland. It had fairly well maintained this reputation until very recently a rival, tri-iodothyronin, has somewhat shaken it. But since tri-iodothyronin belongs to the era of radioactive iodine I shall not consider it for the moment. A decade after Kendall's discovery, Harington[6] demonstrated that the molecular structure of thyroxine is that of a hydroxyphenyl ether of tyrosine containing four atoms of iodine. In the following year Harington and Barger[7] accomplished the synthesis of thyroxine.

These are the most important steps that brought about the concept of thyroid physiology as it existed in 1936, when radioactive iodine appeared upon the scene. The essentials of the concept can be briefly stated. The thyroid gland contains iodine because iodine is an essential ingredient of its hormone. To obtain iodine for the manufacture of hormone, the thyroid gland has developed a special avidity for this element. Without iodine the gland can make no hormonally active material — that is, it cannot perform its function in the bodily economy. Thyroxine had been accepted as the hormone itself, or as an essential component of it.

The other train of discovery took place in the realm of physics. It may be said to have started back in 1789 with the discovery by Klaproth[8] that the mineral pitchblende contained a new element, to which he gave the name uranium. Klaproth's element proved to be an oxide, but in 1841 Peligot[9] isolated uranium in pure form. The discovery, however, that has become of world-shaking importance is that of Becquerel,[10] who in 1896 showed that uranium emits, spontaneously, certain previously unknown radiations detectable by means of photographic plates. Two years later the Curies[11] discovered the naturally radioactive elements radium and polonium. That naturally radioactive elements are useful in medicine is common knowledge; as far as the thyroid gland is concerned, however, these elements have contributed

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nothing to diagnosis, therapeutics or investigation. Radioactive isotopes came into their own in medical research and practice, however, with the discovery by the Joliots[12] in 1934 that various elements can be made artificially radioactive by bombardment with certain particles, permitting the so-called labeling of their atoms.

Early in 1937 the late Karl Taylor Compton addressed a group of students and faculty members at Harvard Medical School on the subject of what aid the methods of modern physics could offer to biology and to medicine. Among other things he mentioned the use of artificially radioactive isotopes. The thought arose that if iodine could be made radioactive, it might provide a tool for the study of thyroid physiology, and perhaps also a new agent in diagnosis and treatment of thyroid disease. The question was put to Dr. Compton, who, after investigation, replied that Fermi, in Italy, had made iodine as well as other stable elements radioactive. Compton further invited the Massachusetts General Hospital thyroid group to undertake a joint investigation of the possible uses of radioactive iodine in collaboration with the Physics Department of Massachusetts Institute of Technology. Professor Robley D. Evans assumed charge of the physics part of the program and obtained the services of a young physicist, Arthur Roberts, who worked full time on this problem, and Dr. Saul Hertz, under my general direction, collaborated with Roberts on the medical aspects. It was a sound partnership of physicists and physicians. This was the starting point[13,14] of joint studies on radioactive iodine that have continued with ever-increasing vigor to date.

At about the same time, and quite independently, P. C. Leblond,[15] in the Laboratoire de Synthèse Atomique in Paris, under the direction of professors Lacassagne and Joliot, began making studies with radioactive phosphorus and iodine, which he subsequently prosecuted with imagination and distinction both in the United States and Canada. Studies on radioactive iodine in relation to the thyroid gland, started early by Hamilton and Soley[16] at the University of California, have also given rise to a long series of important investigations in this field.

Thus research came to a meeting of the ways — one of physiology, and one of physics. This union again fans out in innumerable new ways, and because of the specific avidity of the thyroid gland for iodine, it has been remarkably productive of new knowledge. I know of no example of the uptake of a labeled atom by a particular tissue in any such specific fashion as labeled iodine is collected by the parenchymal cells of the thyroid gland. This specific avidity permits the tracing of the whole process of synthesis of the gland's hormone, and also, in the medical field, makes it possible to plant radiation directly in the cells it is desired to irradiate. The cells collect iodine, and if the iodine is first made radioactive, the cells collect a dose of radiation along with such iodine as is administered. Living tissue cannot distinguish between a stable element and its radioactive isotopes, but, having collected the isotopes, it is subject not only to the chemical action of the element but to that of any radioactive action that the loaded atom conveys.

The situation with which the discovery of radioactivity confronts medicine today resembles that which burst upon it at the turn of the century with the discovery of the role of micro-organisms in the causation of disease. In each case a whole new world of medical potential was suddenly opened. There is, however, this fundamental difference: the micro-organisms were already present but unknown, whereas not only were the radiations emitted by atomic nuclei unknown but also the artificial ones, by definition, were nonexistent.

The physicist has given the physician an instrumentality of colossal power — a power that, if it is to be used for the benefit of man, rather than injury, requires some basic understanding of its nature. But the physician of today knows no more of nuclear physics than the surgeon of Lord Lister's time knew of bacteriology. The surgeon had to learn how to keep bacteria out of the field of his operations. He developed first his antiseptic and then his aseptic technics. Today, the physician using radioactive isotopes must learn how to avoid the injuries that they may cause, while he directs their action to some beneficent purpose. He must develop protective technics against the hazards of radiation comparable to the aseptic technics of the surgeon against bacteria. Everyone is familiar with the aseptic conscience; now there is need of a radiation conscience. To learn enough nuclear physics to develop such a conscience is a great challenge to the physician. Always, he must have his physicist partner at his side to guide him.

The knowledge of nuclear physics that the physician need possess, provided he has the physicist always guiding him and supervising his work, is elementary. The physician's or biologist's role in this partnership is to identify the problems in medicine or biology that the new agent may help solve. He is the one to formulate the questions to be put to nature. The physicist's role is to see that the questions are framed in language that nature can understand and that will not offend her or provoke her to retaliate.

The physician who wishes to work with radioactive isotopes must at least know the following facts:

The first is the structure of atoms— a central core, or nucleus, of positively charged particles called protons, plus a number of uncharged particles, called neutrons. There are also, in a stable atom, a balancing number of negatively charged particles, known as electrons.

Secondly, the nuclei of the very heavy elements uranium (atomic weight 238), thorium (232), radium (226) and so forth — are by virtue of their complexity in an unstable state of equilibrium.

They disintegrate slowly by discharging various component particles of their nuclei into space. It is this process that gives them their radioactivity. The rate of disintegration is steady and follows a logarithmic curve of decay, the so-called half life — that is, the length of time required for half the radiation present at any given time to be lost. Nothing known to man can halt this process, which stops only when all the unstable material has disintegrated.

Thirdly, the naturally occurring stable, nonradioactive atoms of the atomic weight of lead or lighter, can be made unstable, and hence radioactive, by bombardment with beams of various particles, neutrons, protons, alpha particles that are the nuclei of helium atoms and others. An atom so bombarded and rendered radioactive disintegrates until it again attains some stable form. Each particle added to or subtracted from a nucleus changes its atomic weight, so that isotopes are identified by their atomic weights as well as by their half lives.

Fourthly, the use of various forms of bombardment, such as naturally occurring radium or particle accelerators, or by fission of heavier atoms, in the atomic pile, one or more unstable forms of a stable atom such as that of naturally occurring iodine can be produced.

Fifthly, it is necessary that the physician understand the dangers inherent in the use of radioactive materials and the general principle that radioactive contamination will disappear only in terms of the half lives of any radioactive contaminants that may be present.[17] Contaminated material can be removed to a place where it will cause no harm, but nothing will remove its radioactivity but time — measured in terms of half life. For material of short half life a brief wait in a protected place is all that is necessary. For material of longer half life, burial deep in the earth may be the only possible method for safe disposal.

Finally, the detection of radiation, whether for tracer purposes or to discover contamination, is accomplished in a variety of ways that should be familiar to the physician. Contamination with bacteria can be detected by cultural methods. Contamination with radioactive materials can only be detected by discovery of the radiation itself. Man has no sense organ that detects the type of radiation of which I am speaking; he must construct artificial sense organs for the purpose. The photographic plate is one. There are others of various sorts (such as the Geiger counter and the scintillation counter) that can convert radiation into light or sound or electric energy that can be measured and recorded.

So much for general principles. Still to be considered are the isotopes of the elements with which this discussion is concerned — iodine.

When the joint studies of the Massachusetts General Hospital and Massachusetts Institute of Technology began in 1937, use was made of I^{128}, which was obtained from a radium-beryllium source in the days before a cyclotron was available. This material had a half life of but 25 minutes, and therefore could be used only for experiments of not over about one and a half hours.

When the cyclotron at Massachusetts Institute of Technology became available in 1940, it was possible to make I^{130}, with a half life of 12.5 hours. This preparation was far more useful than I^{128}, and with it diagnostic and some therapeutic administrations were made to human beings, as well as more extensive animal experiments. An interesting fact to note in passing is that it was the promise of the early work with I^{128} that made it possible to obtain the funds with which to build the cyclotron at the Institute.

A still more useful isotope, I^{131}, with a half life of 8 days, became available when the United States Atomic Energy Laboratory at Oak Ridge, Tennessee, began making a variety of isotopes by means of nuclear reactors, and distributed them for scientific work to many places far and near. This began in 1946, and I^{131} has been used most frequently in our own investigations and, so I believe, in those of most other workers ever since.

A much more recent and as yet not widely used isotope is I^{132}. This is now being supplied by Brookhaven National Laboratory at Upton, New York. It has a half life of 2.33 hours and is a decay product of tellurium (Te^{132}), which has a half life of over 3 days. It is Te^{132} that is actually distributed, and the I^{132} that gradually forms is drawn off from it. It is claimed that the short half life of I^{132} gives it certain advantages. For examples, it is possible to make frequent tests on the same subject without having to wait a long time for decay, as with I^{131}. Twenty-four hours after the admission of a dose of I^{132} less than 1/1000 of the original activity remains. This short half life also minimizes the problem of disposing of waste material.

It has been suggested that there are other fields than that of the thyroid gland in which I^{132} can be put to good use. These may include the diagnosis and localization of brain tumors, diagnosis of cancer of the liver and determination of blood volumes and blood flow. It has even been suggested that it may have many uses in industry, but those are beyond the scope of this paper.

Still other radioactive isotopes of iodine have been produced, but they have not yet been put to medical or biologic use. Professor Robley D. Evans informs me that up to this year there are a total of 19 whose radioactive properties have been measured. Their atomic weights run all the way from 120 to 139. The only naturally occurring iodine has the atomic weight of 127. This is the only nonradioactive or stable isotope of iodine yet found. The rest — the artificial ones — are all in the state of nuclear uneasiness that causes them to disintegrate. This property is what

gives them their peculiar usefulness to the physiologist, the diagnostician and the therapeutist.

The varieties of use to which radioactive isotopes of iodine can be put are many and constantly increasing.

In the field of physiology the initial work with short-lived isotopes was to determine the laws of iodine collection by the thyroid glands of animals. The actions of various agents that alter the rate of iodine collection by the gland or that of hormone manufacture were made full use of. The first of these was thyrotropin, and this was followed shortly by the ever-growing group of thyroinhibitors — thioureas, thiouracils, sulfocyanates and so forth. Such agents made it possible for the experimenter to accelerate or inhibit the process of hormone manufacture at will, and to set up experiments in ways to yield answers to a great variety of questions. All the steps in the biosynthetic process, previously approached painfully by the involved methods of chemistry, were re-explored more expeditiously and effectively by the use of the labeled atoms.

The methods of following the tracers have also burgeoned luxuriantly. At first one merely counted the disintegration over the thyroid gland directly, or inferred the rate of collection by subtracting from the administered quantity of radiation that which appeared in the urine. Leblond[18] then applied the method of radioautography by which the location of radiation in tissue could be followed at the microscopical level. One could observe not only how much radiation a thyroid gland had collected but also, by means of the radioautograph, exactly where it was located in the cells of the tissue.

The advent of chromatography greatly expanded the potentialities of labeled iodine in physiologic studies. Either with the paper or column type of chromatograph, radioactive-iodine-containing substances in the thyroid gland, blood or other body fluids can be separated one from another and their concentrations determined by measurement of their individual radiation counts. It was by means of such a combination, labeled iodine and chromatography, that Gross and Pitt-Rivers,[19] in 1952, discovered in the thyroid gland the new iodine-bearing amino acid, triiodothyronine, which has given thyroxine such brisk competition for the dignity of being the actual hormone of the gland.

The investigator nowadays not only has the opportunity to give radioactive iodine, and determine to what molecules it becomes attached in vivo, but also can tag various molecules with radioactive iodine in vitro, and thus administer them and follow their fate in the body.

Great new opportunities open up also with the introduction of the newer isotopes that permit the double or multiple labeling of molecules. For example, L. G. Stang, Jr., of the Brookhaven staff, has written to me that it now becomes possible to tag a given molecule in two different places with two (or, I assume, more) different isotopes of iodine, and to observe simultaneously the fates of the two different parts as the molecule undergoes metabolic or other chemical reactions. Also the different reactions and interactions of two different molecules — one tagged, for example, with I^{132} and one with I^{131} — can be studied. The chemistry of iodine is such that a great many things can be tagged with it and a great number of reactions can be investigated.

In the fields of diagnosis and treatment there has also been progress. In that of diagnosis it can be said that, with the combined use of labeled iodine, basal metabolic rate and chemical determination of iodine in the blood, the state of the thyroid function of any human being (or animal, for that matter), healthy or diseased, can be determined with great accuracy. This permits the clinician to get diagnostically oriented in a way never before possible.

In therapeutics, too, radioactive iodine has increased the powers of the physician. I am convinced that it can now be said to be the best agent for treating exophthalmic goiter. Also, in certain forms of thyroid cancer, it offers unique therapeutic benefit. The point that the clinician should bear in mind is that what radioactive iodine offers him therapeutically is the opportunity to destroy in situ cells of thyroid origin, whether hyperplastic, malignant or normal. He can do this by implanting radiation directly within the cells he wishes to irradiate. It is easy to see how superior this approach is to that with the x-ray, with which one must traverse many tissues that one does not wish to irradiate to reach those that one does wish to irradiate. When he considers it desirable the physician now has it in his power to suppress the function of this patient's thyroid gland completely and permanently. The cardiologists sometimes do this to ease the load on the heart. The propriety of such a procedure is not clear to me, and I offer no opinion on it.

The foci of research on the thyroid gland have also multiplied rapidly since the advent of radioactive iodine. It is doubtful if any such intense and growing interest in this organ and its problems would have developed if this new tool for exploring them had not been forthcoming. But one works with what comes to hand, and radioactive iodine is uniquely fitted for exploration of the thyroid gland.

One may speculate on the future use of this agent. When it first became available it was my belief that it would contribute far more to the investigation of thyroid problems than in the fields of diagnosis and treatment. Despite the fact that it has through the years given some new diagnostic procedures, and improved methods for treating certain diseases involving the thyroid gland, I still predict that the greatest contributions of the future will be in the field of research. I cannot foresee much more advance in the field of therapy, but I can see unlimited possibilities in that of research.

References

1. Coindet, J. R. Mémoire sur un nouveau remède contre le goître. Geneva, 1820.
2. Baumann, E. Ueber das normale Vorkommen des Jods im Thierkörper. III. Der Iodgehalt der Schilddrüsen von Menschen und Thieren. *Zeitschr. f. physiol. Chem.* **22**:1, 1896.
3. Marine, D. On occurrence and physiological nature of glandular hyperplasia of thyroid. *Johns Hopkins Hosp. Bull.* **18**:359, 1907.
4. Oswald, A. Gewinnung von 3:5 Diiodotyrosin aus Jodeiweiss. *Ztschr. f. physiol. Chem.* **70**:310, 1911.
5. Kendall, E. C. Isolation in crystalline form of compound containing iodine which occurs in thyroid. *Tr. A. Am. Physicians* **30**:420, 1915.
6. Harington, C. R. Chemistry of thyroxine — constitution and synthesis of desiodo-thyroxine. *Biochem. J.* **20**:300, 1926.
7. Harington, C. R., and Barger, G. Constitution and synthesis of thyroxine. *Biochem. J.* **21**:169, 1927.
8. Klaproth. Cited by Roscoe, H. E., and Schorlemmer, C. *Treatise on Chemistry.* Vol. 2. 1923. Part 1. P. 1149.
9. Péligot, E. Recherches sur l'uranium. *Ann. de chim. et phys.* **5** (Series 3):5, 1842.
10. Becquerel, H. Sur les radiations émises par phosphorescence. *Compt. rend. Acad. de sc.* **122**:420 and 501, 1896.
11. Curie, P., and Curie, S. Sur une substance nouvelle radio-active, contenue dans la pechblende. *Compt. rend. Acad. de sc.* **127**:175, 1898.
12. Curie, I., and Joliot, F. Un nouveau type de radioactivité. *Compt. rend. Acad. de sc.* **198**:254, 1934.
13. Hertz, S., Roberts, A., and Evans, R. D. Radioactive iodine as indicator in study of thyroid physiology. *Proc. Soc. Exper. Biol. & Med.* **38**:510, 1938.
14. Hertz, S., Roberts, A., Means, J. H., and Evans, R. D. Radioactive iodine as indicator in study of thyroid physiology: iodine collection by normal and hyperplastic thyroids in rabbits. *Am. J. Physiol.* **128**:565, 1940.
15. Leblond, C. P., Süe, P., and Chamorro, A. Passage de l'iode radioactif (I^{128}) dans la thyroïde d'animaux sans hypophyse. *Compt. rend. Soc. de biol.* **133**:540, 1940.
16. Hamilton, J. G., and Soley, M. H. Studies in iodine metabolism of thyroid gland in situ, by use of radio-iodine in normal subjects and patients with various types of goiter. *Am. J. Physiol.* **131**:135, 1940.
17. U. S. Department of Commerce, National Bureau of Standards. *Safe Handling of Radioactive Isotopes. (Handbook 42.)* 30 pp. Washington, D. C.: Government Printing Office, 1949.
18. Leblond, C. P. Localization of newly administered iodine in thyroid gland as indicated by radio-iodine. *J. Anat.* **77**:149, 1943.
19. Gross, J., and Pitt-Rivers, R. Identification of 3:5:3'-l-triiodothyronine in human plasma. *Lancet* **1**:439, 1952.

MEDICAL PROGRESS

ESSENTIAL HYPERTENSION: A SELECTED REVIEW AND COMMENTARY

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BOSTON

RECENT developments in the study and treatment of essential hypertension, not necessarily progress, represent established trends, not all good, some interesting, and at least one very important. The unanswered problems of etiology remain. A few therapeutic promises are proving most helpful; others are limited or even useless because of annoying or dangerous side effects; still others remain unfulfilled. These trends are as follows:

The clinical application of nor-epinephrine raises the blood pressure in a manner so similar physiologically to essential hypertension as to qualify almost as its essence.

Interest in the renal origin of essential hypertension, revived twenty years ago by the Goldblatt experiments, has not yet borne therapeutic fruit except for the occasional case of unilateral renal disease, often difficult to diagnose precisely. The hope for a renal extract or renal pressor antigen effective in man has not yet been realized — indeed most cases of essential hypertension are treated as if they were neurogenic.

Statistical studies permit the optimistic to revise upward blood-pressure levels considered normal.

A decreasing use of diet to control disease associated with hypertension is regrettable because this form of management is so effective.

The conservative approach to the surgical treatment of essential hypertension may have progressed too far in reaching almost the vanishing point so far as sympathectomy, unless combined with adrenalectomy, is concerned; this experiment may be watched with lively interest rather than indulged in by most surgeons.

An increasing pressure to use drugs raises the problem of professional huckstering for the hypertensive patient and more particularly for his medical advisers.

Credit is due Goldenberg et al.[1] and von Euler[2] for actually adopting a suggestion made nearly fifty years ago in studying the physiological effects and applying clinically nor-epinephrine, a suprarenal medullary hormone and adrenergic nerve transmitter. It is probably the primary regulator of the blood-pressure homeostatic mechanism since generalized reflex vasoconstriction (or vasomotor action) is closely similar to its intravenous infusion, which reproduces a state very like essential hypertension: elevation of systolic and diastolic blood pressure without increased cardiac output and hence increased peripheral resistance. It is difficult to distinguish some cases of pheochromocytoma with presumed naturally occurring continuous large infusions of mixtures of epinephrine and nor-epinephrine from cases of essential hypertension. The pulmonary hypertension in nor-epinephrine infusion that is not found in essential hypertension, like the failure to find evidence of excessive amounts of nor-epinephrine in blood or urine of patients with essential hypertension, may be due to variations in response or balance of the internal environment in the natural as compared with the experimental state. Indeed, the variation in sub-

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jective symptoms and objective metabolic and circulatory effects, from case to case and in the same case at different times, of pheochromocytoma, of essential hypertension and of normal man, at rest or under stress, may be due to the varying action of the two nonidentical physiologic twins from the adrenal medulla and sympathetic nervous system, epinephrine and nor-epinephrine. Other incompletely controlled or understood variables in natural and experimental hypertension are rate and degree of destruction at site of action (enzyme systems); storage of epinephrine and nor-epinephrine in various organs and tissues; other pressor-depressor systems and their reposed of a hormonal axis on the left and a neural axis on the right, the two connected and integrated at the apex by the circulation, which carries the secretion of the glands, tissue metabolites and the neural hormonal mediators, including nor-epinephrine. The left-hand hormonal axis refers to the pituitary gland, adrenal gland, kidney and other organs and tissues, and the right-hand neural axis to the brain, brain stem, carotid-sinus buffer system, spinal cord and autonomic nervous system.

Most of the particular diseases or conditions readily suggest themselves. Schroeder[3] has described hypertension in obese hairy women with menstrual or

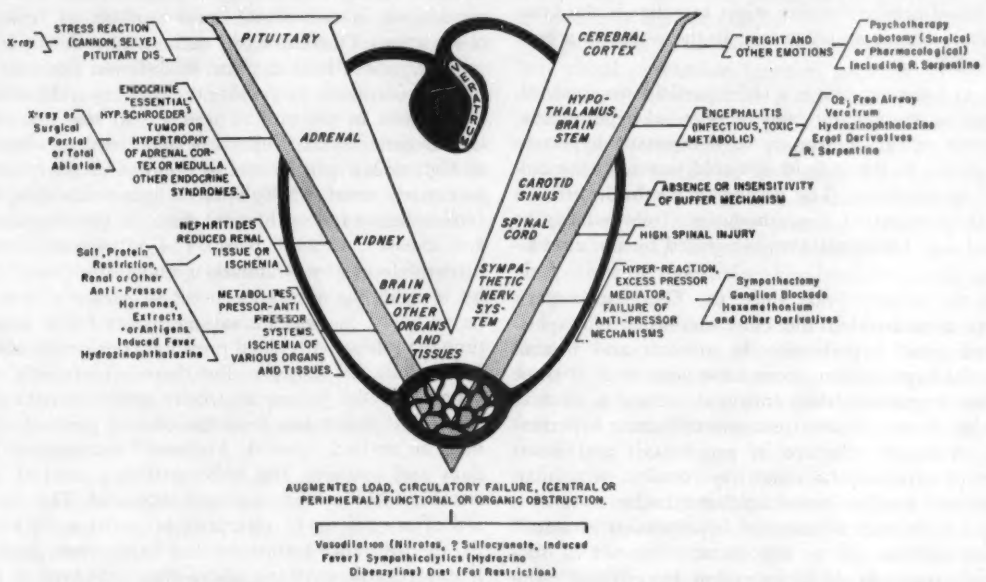
X-ray
STRESS REACTION (CANNON, SELYE)
PITUITARY DIS.
PITUITARY
CEREBRAL CORTEX
FRIGHT AND OTHER EMOTIONS
Psychotherapy
Lobotomy (Surgical or Pharmacological)
Including R. Serpentina
X-ray or Surgical Partial or Total Ablation
ENDOCRINE "ESSENTIAL" HYP. SCHROEDER[3] TUMOR OR HYPERTROPHY OF ADRENAL CORTEX OR MEDULLA. OTHER ENDOCRINE SYNDROMES.
ADRENAL
HYPO-THALAMUS, BRAIN STEM
ENCEPHALITIS (INFECTIOUS, TOXIC METABOLIC)
O2; Free Airway
Veratrum
Hydrazinophthalazine
Ergot Derivatives
R. Serpentina
CAROTID SINUS
ABSENCE OR INSENSITIVITY OF BUFFER MECHANISM
SPINAL CORD
HIGH SPINAL INJURY
NEPHRITIDES REDUCED RENAL TISSUE OR ISCHEMIA
KIDNEY
Salt, Protein Restriction, Renal or Other Anti-Pressor Hormones, Extracts or Antigens, Induced Fever Hydrazinophthalazine
METABOLITES, PRESSOR-ANTI PRESSOR SYSTEMS, ISCHEMIA OF VARIOUS ORGANS AND TISSUES.
BRAIN LIVER OTHER ORGANS AND TISSUES
SYMPATHETIC NERV. SYSTEM
HYPER-REACTION, EXCESS PRESSOR MEDIATOR, FAILURE OF ANTI-PRESSOR MECHANISMS
Sympathectomy
Ganglion Blockade
Hexamethonium
and Other Derivatives
AUGMENTED LOAD, CIRCULATORY FAILURE, (CENTRAL OR PERIPHERAL) FUNCTIONAL OR ORGANIC OBSTRUCTION.
Vasodilation (Nitrates, ? Sulfocyanate, Induced Fever) Sympathicolytics (Hydrazine Dibenzyline) Diet (Fat Restriction)

FIGURE 1. *Diagrammatic Presentation of Alleged Causes of Elevated Blood Pressure, Various Treatments and Some of Their Sites of Action.*

ciprocal action on each other; the state of the nervous system as a whole and of its different parts; and nutritional endocrine and electrolytic constitution. Of the numerous pressor substances referred to in the literature, whether from the adrenal glands, the kidneys or other organs and tissues (some actually identified, and others mere names for physiologic responses), none to date come as close as nor-epinephrine to being the essence of essential hypertension.

A number of actual experimental or pathologic states (nature's experiments) alter the internal environment, causing what may be called homeostatic or secondary hypertension from internal causes. Though the causes are numerous (more than fifty) they account for few (5 per cent) of the patients with hypertension. These causes, as well as other conditions, actual and theoretical, are listed in general terms in Figure 1, which depicts a symbolic V for Victory in the struggle for survival. The V is computerine abnormalities who tend to retain salt and who respond especially well to salt restriction, believing that this group may be separated from essential hypertension of etiology still unknown. The syndrome, he avers, also occurs in men. He thinks that it may account for as many as 20 per cent of his patients with hypertension. This group may represent a partial form of Cushing's disease. Certainly, one encounters a number of patients of this sort in whom a positive diagnosis of full-blown Cushing's disease cannot be made, whose prognosis is relatively good, and who seem to do especially well on salt restriction, as do many hypertensive patients without these signs suggesting an endocrine–that is, adrenal–abnormality.

If nor-epinephrine (or any other pressor substance)[4] proves to be the key in the complicated mechanism for maintaining and elevating the blood pressure in essential hypertension, the question of the primary or initiating cause remains. I have long

looked upon essential hypertension as a "chronic-emergency" response in congenitally susceptible persons.[5] The stress factor is not specific and appears to be the strain of integration or adjustment, uniformity at the expense of individuality, a price exacted by the demands of contemporary cash culture.[6] What I find in the hypertensive population I have since seen described by Riesman et al.[7] in American metropolitan suburbia: an all-pervasive anxiousness for approval, "antagonistic co-operation," the fearful adjustment of people whose character traits are not theirs but the crowd's. This is the second nature of man's own contriving, more hostile than original nature itself.[8] The sympathicoadrenal-renal, salt-retaining, blood-pressure-raising stress response is the same whether one encounters a bear in the woods or a bear on Wall Street.

If, as I suspect, this is a chief participating and initiating cause of many cases of essential hypertension, I choose to call it primary or heterostatic hypertension owing to the individual's cold war with the cultural environment. The psyche or cerebral cortex is the chief organ of this adaptation, followed by the neural and hormonal axes integrated by the circulation.

In the twenty years since the Goldblatt experiments demonstrated the close similarity of experimental renal hypertension in animals and human essential hypertension, there have been at least three serious suggestions that antirenal pressor substances may be effective in the treatment of human hypertension. Although effective in prophylaxis and treatment of experimental renal hypertension in animals as pointed out five years ago,[9] it remains at most a hope for the cure of essential hypertension in man.[10] There continue to be reports and reviews of successful treatment of hypertension by removal of a unilaterally diseased kidney.[11] If done at all, in my experience, operation should be soon after the disease or injury and soon after the onset of hypertension and in young patients or in infants or children with unilateral congenital renal abnormalities and, in general, for urologic indications rather than in the expectation of curing the hypertension. Intravenous or retrograde pyelography may not be sufficient to disclose the rare patient who may be helped by unilateral nephrectomy. Split renal function and in some cases aortography may be required if prior injury, pain or difference in split function points to renal disease, especially when there is not a strong family predisposition to essential hypertension and again if hypertension is definitely established and of recent onset.[12]

Heredity is the etiologic factor in human essential hypertension, amply attested and universally recognized, about which one can do nothing. In the examination and assessment of well or ill persons a carefully taken family history is of primary importance not only in the differential diagnosis of essential and secondary hypertension but also in the recognition of which people with normal blood pressures are predisposed to hypertension. Essential hypertension may be a hereditary disease transmitted as a mendelian dominant with a rate of expression of 90 per cent or more, a strongly positive family history in a given case of hypertension indicating a possible 6:1 chance that the condition is essential hypertension.[13] But the physician must decide what blood-pressure level is high before he decides what to do about it.

Clearly, the level of the blood pressure as determined clinically (indirectly) in the left brachial artery in the sitting or lying position by the auscultatory method, checked by palpation and by observation of oscillations, is one of the most variable of biologic observations. One can easily demonstrate this by having the patient hold the arm in different positions or breathe deeply, or by varying the rapidity and amount of pressure in the cuff. There are so many uncontrolled variables that reports of hypertension, whether of high or low prevalence, in population groups may be entirely unreliable.[14] There is little doubt that, the farther below 140 systolic, 90 diastolic (barring shock and disease), an adult person's blood pressure is consistently found by whatever method, the better risk he is from the insurance point of view — that is, he is likely to pay annual premiums for a longer time than those with blood pressures consistently above 140 systolic, 90 diastolic. But there is increasing evidence that the former are really preferred risks and that the dividing line from the clinical point of view may be revised upward. Fishberg[15] summarizes the data and opinions and believes that a level of 150 systolic, 100 diastolic, is always abnormal. The standard of normal set by insurance actuarial study benefits the insurance companies and harms some patients if one regards anything above their standard as disease. From a study of over 2000 outpatients Hamilton et al.[16] concluded that the average blood pressure rises with age, that this tendency is greater in some persons than in others, that there is no justification other than convenience for drawing a specific line between normal and abnormal, and that "essential hypertension represents no more than that section of the population in which the arterial pressure exceeds an arbitrary value and in which no other disease is found to account for the arterial blood pressure observed."

I conclude from these and my own observations that the blood-pressure level by itself is not an obligatory indication for treatment (especially by hypotensive drugs), nor is the absence of hypertension in vascular disease a contraindication for treatment (especially by diet).

Regardless of the blood-pressure level, diet is almost always the first line of defense of health since obesity exaggerates the level of the blood pressure and increases mortality,[17] because overweight is the one factor in the lethal triad (family history of

renocardiovascular disease, elevation of the blood pressure and overweight) that can be treated successfully with a reduction in excessive mortality[18,19] and finally because weight loss, in my experience, lowers the blood-pressure level of most obese patients with hypertension. Regardless of what one thinks about the relation of cholesterol in the diet to vascular disease, a simple and effective way of reducing calories is to exclude visible fat.

The diet that I recommend for this purpose contains no fat in or on anything, which means no cream, butter, yellow of eggs, cheese (except plain cottage cheese), salad dressing, oil or vegetable or animal shortening (no pie, cake, pastry or fried foods); no pork products (bacon, ham, loin chop or frankfurter), with the fat trimmed from all lean meat; and no oily fish such as mackerel. Water is taken only according to thirst — about six glasses a day. No salt (in cooking or at table as directed) is added to food, and no salted, cured, smoked or canned meat, fish or chicken, skin of chicken, shellfish, canned vegetables or vegetable juices, beets, beet greens, celery, spinach, frozen peas or frozen lima beans are eaten.

When the following sample diet is prescribed the patient is warned to eat exactly what is indicated and not to omit or add items to the menu:

Breakfast:

Fruit or fruit juice (unsweetened).
Cereal (puffed wheat, puffed rice, shredded wheat or low-sodium hot cereals), with skim milk.
Dry toast (may have plain cottage cheese, marmalade or jelly for spread if directed).
Coffee or tea, clear or with skim milk.

Luncheon:

Two or 3 oz. of lean meat, fish (poached in skim milk) or chicken.
Two servings of vegetable, other than potato, without addition of butter, sauce or gravies.
One serving of fruit (unsweetened).

Dinner:

Two or 3 oz. of lean meat, fish (poached in skim milk) or chicken.
Two servings of vegetable, other than potato, without addition of butter.
One serving of fruit (unsweetened).

Diet includes one serving of citrus fruit and at least one serving of green or yellow vegetable daily and at least one serving of liver each week.

Drastic reduction of salt in the diet undoubtedly lowers the blood-pressure level of cases of hypertension corresponding to Schroeder's[3] classification of endocrine hypertension, and in others not so classified one can probably lower the level by desensitizing the vascular system to nor-epinephrine.[20] Salt restriction is conveniently combined with exclusion of fat. Calories may be increased by carbohydrate in patients of normal weight.

The advent of a multitude of blood-pressure-lowering drugs has resulted in a regrettable decrease in the use of diet in general, and the rice-fruit-sugar diet in particular, in severe forms of hypertension. I find it highly effective in Grade 4 malignant hypertension (papilledema), usually with hypotensive drugs. It may be effective in patients with actual or impending cerebral accidents, those with fundal exudates and hemorrhages, those with angina pectoris and those with congestive heart failure, and is safer than the powerful blood-pressure-reducing agents, particularly when insufficiency of cerebral or coronary circulation is present. It is likewise useful in patients with renal impairment provided the possibility of salt depletion is kept in mind.

The patient with significantly impaired psychomotor, visual or cardiac function presents no problem in motivation because he is sufficiently frightened to accept any restriction. When the impairment is minor or not subjectively noted, motivation by one or more successfully treated patients individually or in a group is often effective. This may be done either in a hospital clinic or in private practice. Checking on the salt excretion in the urine, either in the presence of the patient or reported to him later, helps one obtain strict adherence.*

Finally, in the absence of a hundred or more patients in residence on the rice diet as Kempner has, I often show my patients one of his reports[21] with pictures of eyes, heart and blood-pressure levels before and after therapy and allow them to read all details.

For the patient with moderate Grade 2 hypertension (recognized organic change without functional impairment) the indications are reduction of weight if he is obese, moderate salt restriction (500 mg. of sodium) and possibly the milder blood-pressure-lowering drugs if the office pressure is 180 systolic, 110 diastolic, or over. The drugs are more likely to be used the younger the patient under fifty years of age and are of more value in males than in females provided diet alone is not effective. For the patient with mild Grade 1 hypertension (no significant organic change and no functional impairment) the indications are approximately the same but not as rigidly or insistently applied, depending chiefly on diet, especially for the overweight.

Sympathectomy is no longer generally used or accepted as a treatment of hypertension except possibly by Smithwick and his group,[22] who admit 2400 sympathectomies in 3500 patients with hypertension stud-

*An easy procedure for determination of urinary chloride begins with 10 drops of urine in a test tube, to which 1 drop of phenolphthalein, 1 per cent in 95 per cent alcohol, is added. If the urine is alkaline, 10 per cent acetic acid is added drop by drop until the pink from the phenolphthalein just fades. One drop of potassium chromate (20 per cent solution) is then added. With the same dropper, cleaned, used to measure the urine, 1.7 per cent silver nitrate is added drop by drop until the yellow color from the potassium chromate turns to rust. Calculations: (number of drops of silver nitrate used minus 1) times 10 equals milliequivalents of chloride per liter of urine.

Example: with 10 drops of urine and 2 drops of silver nitrate to neutralize the chloride, the urine contains 2 minus 1 (which caused the color change) times 10 milliequiv. of chloride per liter, or 10 milliequiv. of chloride per liter.

ied in the past fifteen years.[22] Like Gibb,[23] I do not look upon sympathectomy favorably because the initial control of the hypertension in 70 per cent or more is only 20 per cent after three years, but one must remember the temporary respite obtainable in this way and probable improved survival when diet and medication are not effective fast enough or are not accepted or tolerated — that is, in malignant hypertension (papilledema), with a particularly accelerated course, provided that renal function is not severely impaired.

Of great interest is bilateral partial adrenalectomy alone,[24] with a reported experience of twenty-two months in 27 patients with malignant hypertension, and combined with sympathectomy,[25] with a reported experience of four years in 125 patients (less than half of them with malignant hypertension), an operative mortality of 22 per cent in the former and 6.4 per cent in the latter. It is now known that relative hypoadrenalism, which will partially or completely control the blood-pressure level in many patients with relieved signs and symptoms in head and heart but not in the kidneys when they are severely damaged, does not by any means ensure against vascular accidents or progress of vascular disease in the vital areas. I have already been chastened by finding evidence of such accidents when hypertensive levels have been controlled by sympathectomy or by hypotensive drugs. The indications for adrenalectomy or adrenalectomy combined with sympathectomy are not established, and the wisdom of inducing Addison's disease, with all the risk and expense of meticulous replacement therapy and management, to ameliorate severe hypertensive cardiovascular disease is not apparent though one can watch with interest the ingenuity with which this combined medical and surgical feat is being accomplished.

Most, if not all, cases of pheochromocytoma reported may give to those who scan the literature a false impression of frequent occurrence. However infrequent, possibly a theoretic 3 or 4 per 1000 deaths in patients with hypertension,[26] one must constantly suspect this diagnosis in the presence of hypertension, continuous or paroxysmal, especially if there are signs and symptoms of hypermetabolism, glycosuria or elevated blood sugar. The clinician must be familiar with all the tests,[27] including presacral oxygen injection for visualization of the tumor[28]; he must remember that no one test is perfect and that these tumors may occur in odd corners of the body (such as the organ of Zuckerkandl[29] and the urinary bladder[30]) if he is to avoid death from a curable disease.

Since all the blood-pressure-lowering drugs (or their forebears with similar properties) have been investigated clinically or generally used for two or more years, there is little to add to the previously reported pharmacologic actions.[31,32] What I have learned to date from approximately 200 reports and my own experience with these drugs is as follows:

Hexamethonium, the chief agent of pharmacologic sympathectomy, may be used if the patient can accept blurred vision, dryness of the mouth, constipation (even paralytic ileus), urinary retention, undue susceptibility to spirits, embarrassing faintness or syncope and impotence; if his doctor is ready to prescribe suitable laxatives, cholinergics (neostigmine, urethane beta-methylcholine), adrenergics (Neo-Synephrine) and the antishock position and to teach the patient or his family to take and record his blood pressure; and finally, if one assumes that venous pooling of the blood and postural hypotension offer a wise and necessary way to treat abnormally elevated blood pressure. Granting these required qualities of mind and heart in patient and physician, I am persuaded that meticulous, detailed, protracted management will equal the achievement of Smirk[33] with methonium salts: in three and a half years' experience, 21 of 28 patients with malignant hypertension survived for twenty-two and eight-tenths months, 7 having died after an average of nine and seven-tenths months; 122 with moderate or severe hypertension had a mortality of 16.4 per cent, as compared with 53 control patients with a mortality of 28.2 per cent, and most patients under sixty years of age with malignant hypertension, cardiac asthma or congestive heart failure returned to work, often without dependence on salt restriction, digitalis and diuretics, together with notable improvement in abnormalities of retina, heart size and electrocardiogram. Clearly, this treatment is only for the worst cases (malignant hypertension and severe hypertension without occlusive disease of the cerebral, coronary or renal circulation).

Pentapyrrolidinium (M & B 2050, Ansolysen), five times stronger than hexamethonium, has been used by Rønnov-Jensen[34] in 48 patients up to seven and a half months. He regards it as the best agent to date in severe hypertension though he considers it dangerous even in experienced hands. He found reduction in blood pressure and side effects about the same as with hexamethonium in 15 patients though the general condition of 7 was considered better on pentapyrrolidinium. Freis et al.,[35] in 27 patients treated for two to six months, had similar results.

A still more powerful drug, SU 3088, has been reported to the American College of Physicians and, as stated by the *New York Times,* is claimed to be superior to hexamethonium and Ansolysen.

I have had no experience with SU 3088, have found pentapyrrolidinium (Ansolysen) in a few trials more powerful than I like in the recommended dosage (starting at 20 mg., or half a tablet) and therefore prefer the half strength now available but still scored to use in a quarter of the original strength per tablet. I use hexamethonium when I must, always with diet, by mouth or by in-

jection, in combination with *Rauwolfia serpentina*, only in malignant hypertension (papilledema) or severe Grade 3 hypertension (fundal exudates and hemorrhages, or congestive heart failure) and when veratrum, usually protoveratrine, is not effective or is not tolerated. It is only given by injection if both the patient and his family are unusually co-operative and stable nervously, and provided the patient can take his own blood pressure or conveniently have it taken and the regimen can be started in the hospital. I have only 1 patient on this regimen at present. The object is to achieve a blood-pressure level of 150 systolic, 100 diastolic, to 170 systolic, 110 diastolic, with symptomatic and objective improvement, particularly in the fundi. I use this drug with the greatest caution, if at all, when there is evidence of cerebral or coronary circulatory insufficiency and expect nothing if renal function is maximally impaired.

I have not had occasion to use hexamethonium or other hypotensive agents to lower the blood pressure in hypertensive crises though they are doubtless effective. I have found deep sedation effective (Sodium Amytal, 0.2 gm. every hour for three doses), and I should consider spinal or even general anesthesia (which I have used once in convulsive seizures) a reasonable procedure in an emergency.

Arfonad, the rapid, short-acting ganglionic blocking agent by intravenous drip, has been used for controlled hypotension in surgery[36] and, I understand, to control hypertension in subarachnoid hemorrhage. In general, controlled hypotension by whatever method in surgery is attended with considerable hazard and many complications,[37] which may be justified by the risk attending spontaneous subarachnoid hemorrhage.

Hydrozinophthalazine (hydralazine, Apresoline) is so mild a hypotensive agent and so active and so powerful in other undesirable directions that neither my patients nor I can tolerate it. Reports in the literature of the ineffectiveness, intolerance and uncomfortable or serious side effects are mounting. The occurrence of a syndrome similar to lupus erythematosus may occur in as many as 9 per cent on prolonged treatment,[38] requiring cessation of the drug or treatment by ACTH or cortisone. In the combined use of Apresoline and hexamethonium, fatal cases not caused by hypertensive complications amounted to 7.6 per cent, the rate of interstitial pneumonia being 5.6 per cent.[39] I believe that this drug will presently fall into disuse.

R. serpentina is the new "phenobarbital," not only in hypertension but in other cardiovascular diseases and in nervous and mental disorders, because its hypotensive effect is mild, its sedative effect is prolonged, but not too profound, and its side effects are tolerable. In my experience the exceptional patient is so depressed (rarely confused) or has dreams sufficiently annoying or is so slowed in tempo as to give up treatment. The looseness of the bowels often noted is usually welcome. The stuffy nose is commonly relieved by an antihistaminic. A pilot study with a double hidden placebo* satisfies me that there is a mild but definite hypotensive action both in the whole drug and in reserpine, and that reported subjective effects in good observers are equally satisfactory in identifying the active substances under the conditions of the clinical experiment.[40]

In acute experiments a single intravenous injection of reserpine appeared to have about the same hypotensive effect as the so-called sedative (Sodium Amytal, amobarbital sodium) test.[41] Indeed, reserpine has been so successful in agitated, resistant, totally unsocial "backward" psychiatric patients, including the mentally retarded, with such marked and, in them favorable, personality changes, as to be hailed as "the most important therapeutic development in the history of psychiatry."[42] If this is borne out, I should be disposed to consider the hypotensive action the side effect and ponder the possible chronic effects of this remarkable drug over the next five to ten or more years in which it may be used in the patients with less severe hypertension, particularly when I note a syndrome like paralysis agitans from large doses[43] and remember the prolonged action and therefore presumed accumulation in the chronic course of treatment.

I combine *R. serpentina*, usually the whole drug, with veratrum, in the form of protoveratrine since it has been available, together with the rice diet at the initiation of treatment in malignant or severe Grade 3 hypertension. If this regimen is successful I first increase the diet progressively to a strict 200-mg. low-sodium diet, in the hope of reducing the drugs if possible, which usually is not successful. The mistake I have made, I think, has been to reduce dietary restrictions too soon, placing too much dependence on the drugs. If protoveratrine is not tolerated or is ineffective, I use hexamethonium or, more recently, pentapyrrolidinium. One of the latter two by mouth with *R. serpentina* probably offers the best combination together with diet in severe cases. Maintaining the diet reduces the amount of drug required, minimizes the development of drug tolerance and increases the hypotensive action, sometimes to an alarming degree.

In mild or moderate hypertension I depend on diet and use *R. serpentina* in most cases on a regimen of a double hidden-placebo investigation both in office and in clinic, stressing the experimental nature of study. This takes the curse off the medicine as a necessity, adds to the day-to-day interest of clinical care and instructs both subject and

*R *serpentina* (Raudixin) and reserpine (Raused) and placebo supplied by E. R. Squibb and Company, New York City.

observer psychologically. In both clinic and office, so far as possible, I employ group treatment with the help of a nurse technician, saving time and money for doctor and patient. Every effort is made to avoid the development of cult practice by emphasis on patient-to-patient motivation in dietary discipline, with spot checking of urinary chloride as a test of dietary adherence.

Of four basic hypotensive drugs or their derivatives, 38 preparations in more than a dozen colors and shades have come to my attention. This count does not include additional dosage forms, syrups or parenteral preparations. Eleven of these are combinations of 2 drugs; 5 are combined with a third, less specific drug. Equally colorful brochures and advertisements present the manufacturers' attractive claims for the various drugs, which may be listed as a composite therapeutic triumph: tranquilizing and sedative, without danger, tolerance or side effects; for the average case, the most effective single hypotensive agent available, significant blood-pressure reduction in 80 per cent; potent long acting, will enable the physician to manage 90 per cent of his cases; for hypertension, angina pectoris, nervousness, neurosis and psychoses. Some find it necessary to stress the innocuousness of their product, and others what it will not do (a negative accent familiar in the advertising script of brewers and cigarette companies).

As with other products, the three most important steps in selling hypotensive agents — contact, arousing interest and creating preference (by marginal differentiation in size, color and packaging) — are done by advertising, the absentee salesman. The sale itself is left to personable callers, the detail men with their samples, their brochures, their succinct and informative words.[44] Advertising of medical products is done via medical journals, by company-sponsored scientific conferences or closed-circuit television programs and through public press releases or special articles. Advertising rates in the medical journals vary from $90 or $100 a page in the research journals to about $1,000 in the *Journal of the American Medical Association*, with extra charges for color and preferred space. In the general medical journals the pages advertising blood-pressure-lowering drugs in a single issue may exceed the scientific articles on hypertension. The cost of a sponsored conference on the treatment of hypertension or of a closed-circuit television panel discussion I do not know, nor do I know the advertising budget of representative drug companies, though I have diligently inquired. I do know that a drug company's expenditure for research may be over $2,000,000 annually and that as much as 10 per cent of gross income may be spent on research. This, I assume, does not include "development," — that is, advertising, — which I should suppose may well be a larger percentage and a larger figure. It must be remembered that the drug companies investigate for the medical profession and discard many unsafe drugs, that they also manufacture and market items auxiliary to health, that they aid research and, above all, that they must make a profit to serve physicians and their patients. Advertising is the accepted way of acquainting the profession and the public with a particular product. A potent urge to advertise the blood-pressure-lowering drugs is provided by the 15,000,000 Americans with hypertension, the potential market. If not 80 or 90 per cent but only half to two thirds should use four hypotensive tablets daily at $5 per 100, the annual value of this market would be $500,000,000 to $750,000,000, an unlikely figure since the total prescription-drug market in 1954 was $1,138,544,000 and that for cardiovascular drugs was $107,493,000. In short, all potential users will not come under treatment.

Nothing in the enormous salesroom that is America is likely to stop advertising or the use of modern means of communication or the employment of doctors, whether or not inadvertently, but always ethically —that is, insistence on the interest not of the doctors or pharmacists but of some hospital or the heart association or of medical science. This ideologic conflict between the market place and clinical science is an example of that antagonistic co-operation which is a culturally induced character trait of hypertensive patients and perhaps of some physicians. Do doctors go too far in lending their names and pictures and even those of their patients to the public press and in releasing data on new drugs to the public before fully informing their fellow practitioners through medical channels?[45-48] Do interviews for the public press keep patients away? Do they aid or harm any doctor-patient relations in a disease or condition whose cause is unknown that is often compatible with many years of healthy life on no treatment at all? In short, if physicians, like the suppliers of drugs, are operating in the illness market, they ought to know it. Probably the greatest single advance in the current treatment of hypertension would be an agreement by the pharmaceutical companies to market all hypotensive drugs in plain, white tablets, inexpensively packaged, accompanied by a sober statement of pharmacologic actions with a like number of matching placebos and an agreement among doctors to make reports to each other. Placebos certainly should not be used in malignant (Grade 4) and probably not in severe (Grade 3) hypertension.

Spurred by the successes of the antibiotics and the steroids, treatment of hypertension has reached a peak of polypharmacy unknown in a hundred years, the absolute opposite of late-nineteenth-century therapeutic nihilism, of which O. W. Holmes[49] was a forerunner. There must be a middle ground between a melancholy meditation on the mortality statistics, which does nothing for the patient, and an eager empiricism, which adds a drug for every 20 mm. of mercury above an arbitrarily set level. One will do well to remember Dr. Holmes's apothegm, "food the

medicine of health, and medicine the food of sickness," which he may have borrowed from an ancient Greek dietician. When drugs are used as Socrates pretended to do in the treatment of brilliant young Charmides's morning headaches (doubtless hypertensive), one should not forget the charm that this wise old man said must accompany it — namely, psychotherapy.[50]

References

1. Goldenberg, M., Pines, K. L., Baldwin, E. deF., Greene, D. G., and Role, C. E. Hemodynamic response of man to norepinephrine and epinephrine and its relation to problem of hypertension. *Am. J. Med.* **5**:792-806, 1945.
2. von Euler, U. S. Physiologic basis for clinical use of noradrenalin. *Ann. Int. Med.* **41**:699, 1954.
3. Schroeder, H. A. *Hypertensive Diseases: Causes and control.* 610 pp. Philadelphia: Lea & Febiger, 1953.
4. *Hypertension: Humoral and Neurogenic Factors: Ciba Foundation Symposium.* 294 pp. Edited by G. E. W. Wolstenholme and M. P. Cameron. Boston: Little, Brown, 1954.
5. Palmer, R. S. Factor of mental stress in essential hypertension. *New Eng. J. Med.* **216**:689-693, 1937.
6. *Idem.* Psyche and blood pressure. *J.A.M.A.* **144**:295-298, 1950.
7. Riesman, D., Denny, R., and Glazer, N. *The Lonely Crowd.* 386 pp. New Haven: Yale University Press, 1953.
8. Patijn, C. L. Responsible society. *Christianity and Crisis* **19**:147, 1954.
9. Palmer, R. S., and Loofbourow, D. Hypertension. *New Eng. J. Med.* **243**:257-265 and 295-307, 1950.
10. Editorial. Pathogenesis of essential hypertension. *J.A.M.A.* **152**: 1435, 1953.
11. Rosenheim, M. L. Treatment of severe hypertension. *Brit. M. J.* **2**:1181-1193, 1954.
12. Howard, J. E., Berthrong, M., Gould, D. M., and Yendt, E. R. Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy. *Bull. Johns Hopkins Hosp.* **94**:51-85, 1954.
13. Editorial. Heredity in essential hypertension. *J.A.M.A.* **136**:254, 1948.
14. Bays, R. P., and Scrimshaw, N. S. Facts and fallacies regarding blood pressure of different regional and racial groups. *Circulation* **8**:655, 1953.
15. Fishberg, A. M. *Hypertension and Nephritis.* Fifth edition. 986 pp. Philadelphia: Lea & Febiger, 1954.
16. Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C. Etiology of essential hypertension: arterial pressure in general population. *Clin. Sc.* **13**:11-35, 1954.
17. Master, A. M., Jaffe, H. L., and Chesky, K. Relationship of obesity to coronary disease and hypertension. *J.A.M.A.* **153**:1499, 1953.
18. Family history and longevity. *Statist. Bull. Metrop. Life Insur. Co.* **35**:1 (September), 1951.
19. Overweight shortens life. *Statist. Bul. Metrop. Life Insur. Co.* 32:1-4 (October), 1951.
20. Raab, W., Humphreys, R. J., Makous, N., DeGrandpre, R., and Gigee, W. Pressor effects of epinephrine, norepinephrine and desoxycorticosterone acetate weakened by sodium withdrawal. *Circulation* **6**:373, 1952.
21. Kempner, W. Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with rice diet. *Ann. Int. Med.* **31**:821-856, 1949.
22. Thompson, J. E., and Smithwick, R. H. Surgical treatment of hypertension. *Cincinnati J. Med.* **35**:203-207, 1954.
23. Gibb, W. E. Sympathectomy in treatment of benign and malignant hypertension. *Brit. J. Surg.* **41**:382-392, 1954.
24. Bowers, R. F. Bilateral adrenalectomy for severe hypertension. *J.A.M.A.* **154**:394-397, 1954.
25. Jeffers, W. A., et al. Further observations on patients with severe hypertension subjected to adrenal resection and sympathectomy. *Ann. Int. Med.* **41**:221, 1954.
26. Soffer, A., Regitine and benodaine in diagnosis of pheochromocytoma. *M. Clin. North America* **38**:375, 1954.
27. Chapman, W. P., and Singh, M. Evaluation of tests used in diagnosis of pheochromocytoma. *Mod. Concepts Cardiovas. Dis.* **23**: 221-224 and 225-228, 1954.
28. Weiman, C. G., Back, K., Russo, P. E., Shoemaker, H. A., and Wolf, S. Diagnosis of pheochromocytoma by demonstration of pressor substances in urine and by retroperitoneal pneumography. *Ann. Int. Med.* **40**:131-139, 1954.
29. Fullerton, C. W., Sutton, J. C., and Milne, I. G. Case of secreting paraganglioma of organ of Zuckerkandl. *Ann. Int. Med.* **40**:1212-1217, 1954.
30. Zimmerman, I. J., Berion, R. E., and MacMahon, H. E. Pheochromocytoma of urinary bladder. *New Eng. J. Med.* **249**:25, 1953.
31. Hoobler, S. W., and Dontas, A. S. Drug treatment of hypertension. *Pharm. Rev.* **5**:135-174, 1953.
32. Meilman, E. Medical management of arterial hypertension. *New Eng. J. Med.* **248**:894-902, and 936-943, 1953.
33. Smirk, F. H. Results of methonium treatment of hypertensive patients: based on 250 cases treated for periods up to 3½ years, including 28 with malignant hypertension. *Brit. M. J.* **1**:717-723, 1954.
34. Rønnov-Jensen, V. Medical treatment of arterial hypertension: pentapyrrolidin bitartrate (Ansolysen) new agent for oral therapy. *Ugesk. f. laeger* **116**:551-558, 1954.
35. Freis, E. D., Partenope, E. A., Lilienfield, L. S., and Rose, J. C. Clinical appraisal of pentapyrrolidinium (M&B 2050) in hypertensive patients. *Circulation* **9**:540-546, 1954.
36. Little, D. M., Hampton, L. J., and Grosskreutz, D. C. Use of Arfonad in modification of technique of controlled hypotension. *Surgery* **35**:857-866, 1954.
37. Stone, H. H. Controlled hypotension during surgery. *Maryland M. J.* **3**:163-166, 1954.
38. Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H. Rheumatic and febrile syndrome during prolonged hydralazine treatment. *J.A.M.A.* **154**:23-29, 1954.
39. Morrow, J. D., Schroeder, H. A., and Perry, H. M., Jr. Studies on control of hypertension by Hyphex. II. Toxic reactions and side effects. *Circulation* **8**:829-839, 1953.
40. Palmer, R. S. Unpublished data.
41. Tuchman, H., Sletten, I. W., and Crumpton, C. W. Clinical study of effects of intravenous reserpine (Serpasil) in hypertensive patients. *Am. Heart J.* **48**:449-454, 1954.
42. Noce, R. H., Williams, D. B., and Rapaport, W. Reserpine (Serpasil) in Management of mentally ill and mentally retarded. *J.A.M.A.* **156**:821-824, 1954.
43. Weber, E. Rauwolfia alkaloid in psychiatry: similarity of its effect to that of chlorpromazine. *Schweiz. med. Wchnschr.* **84**:968-970, 1954.
44. Mills, C. W. *White Collar: The American middle classes.* 378 pp. New York: Oxford, 1951. P. 161.
45. *United States News & World Rep.* **34**:28-32 (August), 1954.
46. *Saturday Evening Post* **226**:26 (June 5), 1954.
47. *Reader's Digest* **65**:31-36 (August), 1954.
48. *Colliers* **133**:58-61 (March 5), 1954.
49. Holmes, O. W. *Teaching from the Chair and at the Bedside: An introductory lecture delivered before the medical class of Harvard University, November 6, 1867.* 45 pp. Boston: David Clapp & Son, 1867.
50. Charmides, or Temperance. In *The Dialogues of Plato.* (Transl. by G. Jowett.) New York: Random House, 1937. Vol. 1. P. 3.

MEDICAL INTELLIGENCE

NEEDLE BIOPSY OF THE PARIETAL PLEURA*

A Preliminary Report

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THE entity of serofibrinous pleurisy presents many obstacles to diagnosis. Difficulties are often encountered in the isolation of the *Mycobacterium tuberculosis* from the sputum, gastric washings and pleural fluid in the tuberculous patient. In addition, aspiration biopsy of pleural fluids frequently yields samples consisting of distorted cells that may not be sufficiently representative pathologically for definitive microscopical diagnosis. Often, specific therapy must be instituted before definitive bacteriologic diagnosis can be established.

The purpose of this report is to describe a simple method for needle biopsy of the parietal pleura that may obviate prolonged and costly diagnostic procedures and even, in some cases, exploratory thoracotomy.

To our knowledge no case of parietal pleural biopsy by this method has previously been reported.

MATERIALS AND TECHNIC

The materials necessary are an ordinary thoracentesis tray, with the addition of a Vim–Silverman biopsy needle, two sterile Kelly clamps, a scalpel and black-silk suture.

The patient is premedicated with Demerol and a barbiturate. The biopsy site, which is previously determined by x-ray and fluoroscopic examination of the chest, is prepared with tincture of Merthiolate and alcohol. Two per cent Novocain is used for local anesthesia, which is carried down to the pleura. With the patient in the sitting position, a small skin incision is made at the biopsy site and a 17-gauge needle, to which a 50-cc. syringe is attached, is inserted into the appropriate interspace along the upper margin of the lower rib. Constant traction is applied on the plunger of the syringe while the needle is advanced. At the first sign of withdrawal of pleural fluid, the needle is withdrawn a fraction of an inch and a Kelly clamp is applied to the shaft of the needle adjacent to the skin. The needle is then withdrawn completely and the same distance (from Kelly clamp to tip) is measured off on the Vim–Silverman needle with the biopsy shaft inserted. A Kelly clamp is applied to the biopsy needle marking off this distance. The biopsy shaft is then withdrawn, and the obturator is inserted. The needle is advanced through the skin incision to the distance marked off by the clamp. The obturator is removed, the biopsy shaft inserted, the clamp removed, and the outer needle carried forward approximately 1.9 cm. while the biopsy shaft is held in place. Both portions of the needle are now rotated through 360° and withdrawn together. The biopsy shaft now encompasses the sample of tissue. The skin is closed with one silk suture, and a sterile dressing applied.

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CASE REPORTS

CASE 1. A 54-year-old Negro was admitted to the medical service with complaints of cough and hemoptysis. He had been well until 5 weeks previously, when a vigorous cough productive of rusty sputum, occasionally with bright-red blood, developed. There had been a weight loss of approximately 13.6 kg. in the year before admission.

Physical examination revealed a well framed, muscular man. The left hemithorax was dull to percussion from apex to base. Tactile fremitus and breath sounds were absent in this area. Wheezing without frank rales was heard over the right side of the chest. The trachea was displaced to the right, and the liver edge was just palpable below the right costal margin.

The temperature was 101°F. The blood pressure was 150/90.

Studies of the blood showed a red-cell count of 4,080,000, with a hemoglobin of 12.5 gm. per 100 cc., and a white-cell count of 4250, with 6 per cent band forms, 35 per cent neutrophils, 53 per cent lymphocytes, 1 per cent eosinophils and 5 per cent monocytes. The sedimentation rate was 40 mm. in 1 hour. The blood Kahn reaction was negative. The cephalin flocculation was negative, and the thymol turbidity 1 Maclagen unit. X-ray examination of the chest revealed a diffuse effusion on the left, which resulted in displacement of the mediastinal contents to the right. A thoracentesis yielded 1500 cc. of cloudy, yellow fluid. During the thoracentesis it was noted that the pleura was quite thickened. Repeat films of the chest, plain and Bucky, disclosed pleural effusion to the level of the 3d rib anteriorly. No underlying pulmonary disease could be demonstrated. Examination of the pleural fluid failed to demonstrate any organisms on smear or culture. The protein content was 30 gm. per liter. Examination of the sputum, including 24-hour and 72-hour concentrates, was repeatedly reported as negative for acid-fast bacilli, as were bronchial secretions and gastric washings. Papanicolaou smears of sputum and pleural fluid, as well as cell block of pleural fluid, contributed nothing. Urine cultures were also negative for tuberculosis. A pleural biopsy was then performed. Microscopical study of the specimen revealed tuberculous granulation tissue (Fig. 1). Three months after admission a repeated thoracentesis yielded fluid that finally demonstrated tubercle bacilli on culture.

CASE 2. A 35-year-old Negress was admitted to the medical service with complaints of cough. She had been relatively well until 3 months previously, when a persistent cough, productive of thin whitish sputum, developed. She denied hemoptysis, but admitted a 6.8-kg. weight loss in the 3 months before admission.

Physical examination showed a poorly nourished and somewhat emaciated woman. A few nontender cervical lymph nodes were palpable bilaterally. Amorphic breathing

was noted over the left apex, with a few crackling rales over the right apex. Bronchial breathing was heard over the right base posteriorly. Examination of the blood revealed a red-cell count of 2,440,000, with a hemoglobin of 7.5 gm. per 100 cc., and a white-cell count of 5700, with 84 per cent mature neutrophils and 16 per cent lymphocytes. The sedimentation rate was 81 mm. in 1 hour. The blood Kahn reaction was negative. The total protein was 6.8 gm. per 100 cc., with an albumin of 2.8 and a globulin of 4.0 gm. X-ray study of the chest disclosed a linear and nodular infiltration of the upper half of the left-lung field, with cavitation; the right-lung field showed a linear and patchy infiltration with some cavitation. The horizontal fissure was thickened, and a density, interpreted as pleural effusion, was noted on the right. Repeated examinations of the sputum, including 24-hour and 72-hour concentrates, were negative for acid-fast bacilli and fungi. A thoracentesis yielded about 100 cc. of straw-colored fluid, which had a specific gravity of 1.018 and a protein content of 40 gm. per liter. Smear and culture of this fluid were negative for fungi and bacteria. A repeat film of the chest in the upright and lateral decubitus position failed to show any change in the contour of the homogeneous density at the right base that had previously been reported as pleural fluid. It was then believed that this density was indicative of thickened pleura. A tuberculin skin test was markedly positive in a dilution of 1:10,000. Coccidioidin and histoplasmin skin tests were negative. A pleural biopsy demonstrated caseation necrosis and multinucleated giant cells consistent with tuberculous pleuritis. Subsequently, laryngoscopy was performed because of development of hoarseness. An infiltration was noted in the region of the epiglottis, which, on biopsy, revealed tuberculosis. At no time were tubercle bacilli seen on smear or culture of sputum, pleural fluid or laryngeal aspirate.

Discussion

The method described is a simple one. The hazards are the same as those associated with simple thoracentesis. In a series of 6 biopsies performed on suitable candidates in this institution, pleura was obtained in each. No case of hemorrhage, pneumothorax, pleural contamination or sinus-tract formation has been encountered as a complication. This method not only is advantageous in the diagnosis of serofibrinous pleurisy, but also may be applied to the diagnosis of pleural masses. The samples obtained are clear and are as suitable for microscopical analysis as tissues obtained by needle biopsy of the liver, lung and kidney.

The advantage, as demonstrated in the 2 cases described above, is that of an expedient method of diagnosis that is safe. The diagnosis of tuberculosis was made in Case 1 long before culture of the pleural fluid demonstrated tubercle bacilli and in Case 2 before invasion of the epiglottis had occurred.

The danger of lung puncture is obviated by the fact that the measurements on the Vim–Silverman needle are taken with the biopsy shaft in place; this distance from the skin is entirely within the confines of the parietal pleura.

This procedure is not recommended for patients with minimally thickened pleura. In our experience attempts at biopsy in such cases often yield not a sample of pleura but one of intercostal muscle. This is due to the short distance that the needle must traverse to reach the pleural space. In these cases the outer needle is not sufficiently anchored, and the biopsy shaft must, of necessity, include muscle and fat not previously penetrated by the obturator-equipped needle. Even if a sample of pleura is obtained in these patients it is frequently lost on withdrawal because it occupies the distal tip of the biopsy shaft; in addition the danger of lung puncture, with its attendant sequelae, is enhanced. It is recommended that this procedure be used with caution when the visceral pleura is not separated from the parietal pleura by pleural fluid; however, if the pleura is maximally thickened, a representative sample may be obtained safely without pleural fluid as a guide. We do not advocate biopsy of the visceral pleura or lung by this technic.

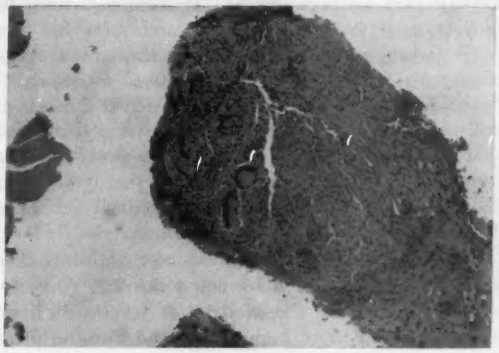

FIGURE 1. *Several Large Multinucleated Giant Cells of Langhans, Showing Typical Peripheral Distribution of the Cell Nuclei.*

Considerable dense fibrous tissue reaction is also present.

It appears that this method is most informative in patients with thickened pleura without pleural effusion and with or without demonstrable underlying pulmonary disease. It may also represent, in some cases, the only method of pathological diagnosis in a primary pleural mass without actual thoracotomy.

The procedure is painless, with a minimum of discomfort to the patient.

Summary

Two cases of tuberculous pleuritis are presented in which the diagnosis was established by needle biopsy of the parietal pleura. The technic of pleural biopsy is described, and the hazards, indications and advantages of this method are discussed.

DOCTORS AFIELD

George Logan — Agrarian, Pamphleteer, Amateur Diplomat

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ON the basis of the first twenty-eight years of George Logan's life one would have predicted a sedate and successful career for him as a Philadel-

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phia physician. Indeed, he had all the necessary qualifications: a famous Pennsylvania name, an independent fortune, an unparalleled medical education and a will to succeed. Yet his life took him far afield from medicine into the political arenas of the day, caused him to be expelled from the Society of Friends and labeled a seditionist by the press, and even inspired the Congress of the United States to enact a law expressly aimed at him.

Logan was born in 1753 into a rich and influential Philadelphia Quaker family. It seemed natural for him to turn to medicine as a career, for his forebears were established among the city's great physicians; his own father was heir to a medical library of 600 volumes, which far exceeded the meager collection of the Pennsylvania Hospital itself, and young Logan read avidly in it. He was sent to England for his formal education after the age of fourteen, and matriculated in the medical school at Edinburgh in 1776.

He did well in his medical courses, and during his final year was honored by being the first American chosen president of the Medical Society — an honor that he prized more highly than the Edinburgh degree itself. However, as seems typical of medical students of all eras, Logan held a poor opinion of the worldliness of the medical faculty; at one point he cried out in a letter that the Edinburgh lectures were "more calculated for the physician as a philosopher than as a practitioner."[1]

He immediately established himself as a successful doctor in Philadelphia and, during his second year of practice, achieved the praises of Benjamin Franklin himself for curing him of his crippling gout by using a diet high in grains and low in meat and spirits. Logan was only in active practice for three years, however. A pregnant wife and an untended ancestral estate forced him to pay more attention to his family than he considered possible in his profession, and at this time he therefore moved 6 miles out from Philadelphia to become a country squire.

Once oriented toward the problems of agriculture in the late eighteenth century, he soon became incensed at the attitude of the federal Government toward the farmers of the country. Although the population was predominantly rural at the time, the Government seemed primarily oriented toward the mercantile interests of the eastern seaboard. There was good reason for this, for the nearly bankrupt government was trying to appease the merchants who had underwritten most of the cost of the recent revolution and who now demanded their money back at full value. The farmers, including Logan, most of whom had never had any money anyway, naturally urged a cheap-money policy, which was turned down by the Government. Furthermore, a law was soon passed designed to tax the farmers' lands and grain products (whiskey!) to pay the merchants off.

Logan was soon hurrying over the countryside urging the farmers to rebel against these alleged injustices. When his speechmaking failed to stir the lethargic farmers to action he turned to a favorite device of the times — the pamphlet. In five pamphlets entitled "Letters Addressed to the Yeomanry of the United States," which were widely circulated and decidedly incendiary in tone, he cried:

> Congress is establishing a system of finance, founded in deception . . . Come forward . . . it is you who must feel the effects of their Machiavellian politics . . . How long will you suffer yourselves to be duped by the low cunning of half-informed lawyers and mercenary merchants?[2]

Although Logan sought anonymity by using a pseudonym, his authorship became widely known. The Government was enraged, and its press stated that the doctor "consorted daily with dangerous radicals from the west . . . men of no family, no property, and no principles."[3] The quiet Quakers expelled him from the Society. However, the "dangerous radicals from the west," being simple farm folk who understood his message if not his allusions, rewarded him with a seat in the Pennsylvania Legislature.

With acts such as these Logan became a recognized foe of the Government. Soon his great estate became the meeting place of political refugees from Europe bent on introducing the new French radical republicanism into America along with political outcasts from all over the eastern seaboard who harbored grudges against the Federalists. Before long Logan was an arch Francophile and was suspected of treasonable tendencies.

In 1793 war broke cut between England and France, and, to George Logan's dismay, the United States signed a defense treaty with England in direct violation of a previous pact of mutual trust executed with France in 1778. The embittered French retaliated by placing an embargo on American shipping in Europe, seizing American property in France and mounting a naval blockade off the eastern coast of the United States. The startled United States in turn developed a war hysteria; funds were immediately appropriated for defense, and General Washington was called from retirement to raise an army to repel any invading Frenchmen.

Logan was greatly upset at the wave of anti-French feeling that swept over the country. He was further suspicious that the dispute was being deliberately fostered by mercantile interests bent on enriching themselves in the armament race. Certain that the French did not want war with the United States, he determined to go to Europe and singlehandedly appease the French. Although he left the country secretly on his trip, his political opponents soon discovered his absence from the country. The *Philadelphia Gazette* observed editorially:

> There cannot be the least question but the Doctor, from his *inordinate* love of *French liberty*, and hatred to the

> sacred constitution of the United States, has gone to the French Directory, fraught with intelligence of the *most dangerous tendency to this country. Their* demagogue is gone to the Directory for purposes *destructive of your lives, property, liberty, and holy religion.*[4]

President John Adams dispatched secret agents after Logan, but apparently owing to the difficulties of travel of the day none came close to intercepting him and he arrived in Paris unconscious of the uproar boiling behind him. Not only did he soon convince himself that the last thought in the average Frenchman's mind was war with the United States (the only thought in most Frenchmen's minds being the war with England) but also he carried off a diplomatic coup befitting a Walter Mitty. With great difficulty he obtained an interview with Talleyrand and the members of the Directory and was able to extract from them a paper testifying to their pacific intentions toward the United States. The French further promised Logan to release all interned United States shipping and citizens and to call off their western Atlantic naval blockade.

Arriving back in the United States with his paper, the naïve doctor soon found his supposed triumph viewed by the federal Government with the greatest of suspicion. General Washington, still busy training the militia, received Logan coldly and sarcastically observed how singular it was that a private person should himself be able to accomplish what "gentlemen of the first respectability [that is, United States Secretary of State Timothy Pickering] especially charged under the authority of the government" were unable to do.[5] Congress dismissed any French proposals that might be transmitted by individuals without public character or authority. As a final insult, in January, 1799, the Senate passed a bill, popularly known as "Logan's Act," providing for a fine and imprisonment for any citizen who thereafter engaged in diplomatic negotiations without official governmental license.

In spite of the uproar Logan had the satisfaction of watching the United States re-establish diplomatic missions with France within two weeks of the passage of the Logan Act. Apparently, he also suffered little political consequence, for he was almost immediately re-elected to the Pennsylvania Legislature and a year later was appointed to the United States Senate, where he sat for six years. He continued active in political affairs until, at the age of sixty-seven, he suddenly succumbed to dropsy and a "fit."

The Logan Act is still the law of the land and is even today the primary legislative act regulating unauthorized diplomatic intercourse between American citizens and foreign powers. Although no one has ever been convicted under its provisions, it is still dusted off from time to time — usually for partisan political purposes.

References

1. Tolles, F. B. *George Logan of Philadelphia.* 362 pp. New York: Oxford University Press, 1953. P. 35.
2. *Idem. George Logan of Philadelphia.* 362 pp. New York: Oxford, 1953. Pp. 113 and 114.
3. *Idem. George Logan of Philadelphia.* 362 pp. New York: Oxford, 1953. P. 129.
4. Logan, D. N. *Memoir of Dr. George Logan of Stenton.* 207 pp. Philadelphia: Historial Society of Pennsylvania, 1899. Pp. 59 and 60.
5. Tolles, F. B. *George Logan of Philadelphia.* 362 pp. New York: Oxford, 1953. P. 178.

Massachusetts Physicians Art Society

39. *Sabina Canyon, Tucson, Arizona*

Oil Painting by

Fritz B. Talbot, M.D.

Formerly, Chief, Children's Medical Service
Massachusetts General Hospital

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 41221

PRESENTATION OF CASE

First admission. A seventy-two-year-old lawyer was admitted to the hospital because of blood-streaked stools.

One month previously he noted slight anal bleeding. Ten days before admission his lifelong constipation had disappeared, and his bowels moved every day without the customary laxatives. Two days previously, after a bland supper, he had the sudden onset of sharp epigastric pain and nausea. The pain persisted through the night, interfering with sleep. He had had no diarrhea, emesis, chills or fever.

Six years before admission he had a sudden onset of substernal and infraxiphoid pain, which lasted thirty minutes and recurred two days later. The left ventricle was slightly prominent. An abdominal film showed a group of calcifications in the right upper quadrant in the region of the gall bladder. A Graham–Cole test demonstrated minimal filling; the calcifications were not definitely visualized.

Physical examination revealed a well developed man, who did not appear ill. Examination of the heart and lungs was negative. The abdomen was slightly distended and tender to palpation just to the left of the umbilicus. Examination revealed a large, firm, nontender fungating mass on the anterior wall of the rectum, just superior to the prostate. The prostate, which was of normal consistence, was smooth and enlarged to twice the normal size. There was bright-red blood on the examining finger.

The temperature, pulse and respirations were normal. The blood pressure was 170 systolic, 80 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 13.8 gm. per 100 cc. and a white-cell count of 19,800, with 84 per cent neutrophils. The nonprotein nitrogen was 32 mg., and the serum amylase 13 Russell units per 100 cc. The prothrombin time was 100 per cent. A stool gave a ++++ guaiac test. An electrocardiogram showed a normal tracing. A plain film of the abdomen demonstrated a large amount of gas in slightly dilated loops of small intestine and considerable fecal material in the ascending colon. The lung fields were clear, and the heart was unchanged from the examination six years previously. A barium-enema examination showed numerous diverticula in the sigmoid and descending colon, and again the multiple areas of calcification in the region of the gall bladder. Sigmoidoscopy to 20 cm. revealed a large, fungating mass on the anterior wall of the rectum, and a biopsy was reported as showing adenocarcinoma.

On the day of admission the patient had sudden severe colicky pain, mostly in the right lower quadrant. The pain was intermittent and associated with much sweating; it was more severe than the pain he had had before hospitalization. The abdomen was slightly distended and tympanitic, quiet and nontender. The pain was relieved by Demerol. The serum bilirubin on this day was 0.8 mg. and on the following day 1.9 mg. per 100 cc. On the third and fourth hospital days he had similar episodes of right-upper-quadrant colicky pain. On the fifth hospital day a cholecystectomy and choledochostomy were performed. The gall bladder showed subacute and chronic inflammation, and two 5-mm. faceted stones and stone fragments were washed out of the common duct. There was no evidence of pancreatitis or metastatic disease. The patient had an uncomplicated convalescence. A cholangiogram was negative, the T tube was removed, and he was discharged on the eleventh postoperative day.

Second admission (two weeks later). In the interim he had felt well. He had been up and about each day, had a good appetite and had had no further episodes of pain.

Physical examination was unchanged. The hemoglobin was 12.2 gm. per 100 cc. The white-cell count was 8600, with 83 per cent neutrophils. The nonprotein nitrogen was 27 mg. per 100 cc. The prothrombin time was 16 seconds (normal, 13 seconds).

On the third hospital day a combined abdominoperineal resection was performed. During the last thirty minutes of the operation the patient was hypotensive, and 1000 cc. of whole blood was given. The postoperative course was complicated by signs of intestinal obstruction, and on the fifth postoperative day, because of a mechanical obstruction of the terminal ileum, a side-to-side enteroenterostomy was performed; 500 cc. of whole blood was given during the procedure. The postoperative course was again complicated by nausea and vomiting. Barium, introduced through the Miller–Abbott tube, outlined an area of narrowing in the ileum just distal to the tube. Barium progressed slightly in the small bowel, and very little reached the colon. Narrow loops of small bowel were seen in the pelvis and right lower quadrant. Five days

after the enteroenterostomy a Witzel enterostomy was performed under local anesthesia. The patient slowly improved and was discharged on the thirty-second hospital day.

Final admission (seven weeks later). He had been well in the interim, until one week previously, when he noted weakness, anorexia, nausea, hiccups and diarrhea. Four days before admission, when he returned home from work, he called his family physician. Jaundice was evident. A perineal abscess ruptured and drained foul, bloody pus. He became progressively weaker and drowsier and was finally prevailed upon to enter the hospital.

Physical examination revealed a drowsy, icteric man. There was slight edema of the back, abdomen and ankles. The tongue was dry. The lungs were clear. The liver edge was not definitely palpable, but the margin was thought to be 3 fingerbreadths below the right costal arch. The colostomy was functioning well; the abdomen was soft and quiet. The spleen was not felt. The perineal wound was draining yellow, serous fluid.

The temperature was 101°F., the pulse 100, and the respirations 20. The blood pressure was 135 systolic, 75 diastolic.

The urine had a specific gravity of 1.020 and gave +++ tests for bile and albumin; the sediment was bile stained and contained 200 red cells and 50 white cells per high-power field, as well as numerous bacteria. Culture showed abundant coliform organisms. Examination of the blood revealed a hemoglobin of 12.6 gm. per 100 cc. and a white-cell count of 17,100, with 88 per cent neutrophils. The prothrombin time was 27 seconds (normal, 13 seconds). The nonprotein nitrogen was 26 mg., and the serum bilirubin 23.4 mg. per 100 cc.; the serum sodium was 128 milliequiv., the potassium 5.5 milliequiv., the chloride 99 milliequiv., and the carbon dioxide 26 milliequiv. per liter. The alkaline phosphatase was 8.1 units. Cephalin flocculation four days before admission was ++++.

The patient was given 500 cc. of whole blood. He became progressively more drowsy but could easily be roused, and was rational. The liver edge three days after admission was palpable at the right costal arch. On the third hospital day he became comatose and oliguric and died.

Differential Diagnosis

Dr. Perry J. Culver*: This long and complicated case has several definite conditions that I shall discuss briefly and then go on to the major problem, which is, "What brought about the death?" The story of the cancer of the rectum is characteristic. I think the diarrhea, which began after a period of constipation, was produced by the same mechanism as a fecal impaction — that is, partial obstruction of the bowel has a tendency to increase peristalsis so that constipation changes to diarrhea.

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The diverticula demonstrated in the x-ray films apparently were never very symptomatic although they may have contributed to the constipation via a so-called spastic colon. The first of the episodes of chest pain, which occurred six years previously, may have been an attack of coronary occlusion, but electrocardiograms were normal. Characteristic features of cholelithiasis and cholecystitis were the subsequent attacks of pain, usually in the right upper quadrant, but once in the right lower quadrant, with tenderness to the left of the midline, calcifications in the right upper quadrant and the development of jaundice and leukocytosis. Possibly, there was a stone in the common duct, perhaps with acute cholecystitis superimposed, and that was the reason for the first operation.

On the first admission the finding of rales at both bases was probably not significant in view of the fact that the x-ray films were normal and the heart was not enlarged. The heart murmur, the wide pulse pressure and the age of the patient make me suspect that he probably had arteriosclerosis of the aortic valve that was probably not severe.

The change in the urine is of considerable interest to me. On the first admission the urine was normal; on the second admission it contained some albumin, with white cells and a few red cells in the sediment. The possibility that infection was introduced with a catheter at the time of the first operation has to be considered. I am thinking especially of prostatitis secondary to bladder infection. I suppose that a lesion on the anterior wall of the rectum could have involved the prostate gland. Pyelonephritis is another, though less likely, possibility. After the combined abdominoperineal resection and the development of a perineal abscess, which I assume was a collection of pus in the perineal wound, there were marked changes in the urine, — namely, many pus cells, many red cells and a great deal of albumin, — which makes me think that prostatitis of a more severe degree secondary to the infection in the perineal area had developed. The infection in the perineal area may have accounted partly for the increased white-cell count and the fever on admission. Again, I cannot rule out pyelonephritis although the fact that the specific gravities of the urine were quite high is against it. That is as far as I should like to discuss the urinary picture.

The complications of the combined abdominoperineal resection need little comment. They added stress to this already difficult situation.

The major problem is, What was going on in the liver? This man had several possible causes for jaundice. He had a carcinomatous lesion in the rectum, which notoriously metastasizes to the liver. The liver was at least grossly free of metastases at the time of the combined abdominoperineal resection eleven weeks before the last admission. I suppose, however, that metastases to the liver could have occurred in that period. Several things are against metastases as

an explanation for the jaundice. The liver was not very large; with metastatic liver disease severe enough to cause death fairly rapidly the liver is usually tremendously large and hard. Secondly, the alkaline phosphatase was not elevated. If any test is of value in confirming the presence of metastatic disease in the liver it is probably an elevated alkaline phosphatase that is out of proportion to abnormalities in other liver-function tests. One of the hallmarks of metastatic liver disease is the bizarre nature of and lack of any correlation between the various liver-function tests. There were not many such tests done here. The cephalin flocculation of ++++ may be seen in metastatic disease of the liver, but it is rare. On the basis of lack of enlargement of the liver and the normal alkaline phosphatase I think that metastatic liver disease did not play a fundamental role in the death. If there were metastases to the liver, they were incidental.

What role did the gallstones and the chronic cholecystitis play in the ultimate clinical course? The negative cholangiogram suggests that there was adequate drainage in the biliary tree so that obstruction played no part in aggravating liver disease. Sometimes, a stone may be missed in the cholangiogram, and there is partial obstruction to the biliary tree. Such obstruction could explain part of the jaundice, the fever, the leukocytosis and the remainder of the picture. In such a case there should have been considerably more elevation of the alkaline phosphatase, but not a ++++ cephalin flocculation or such a prolonged prothrombin time. Consequently, I think that there is very little in favor of partial obstruction in the biliary tree as a cause of the jaundice, and certainly there is no reason to suspect that obstruction per se could have brought about death so rapidly.

The third likely cause of the jaundice is intrahepatic or hepatocellular liver disease; I might be even more specific and call it hepatitis, perhaps of a viral type. The jaundice occurred eleven weeks after this man had received several transfusions. The incubation period of the so-called virus of homologous serum jaundice is from six weeks to six months so this eleven-week period fits quite nicely into the proper incubation period. The evidence of hepatocellular dysfunction on the basis of the liver-function tests and the history is quite manifest. This man was icteric, he was drowsy, he had a ++++ cephalin flocculation, and he had a prolonged prothrombin time. The serum albumin was not mentioned, but since there was edema of the back, abdomen and legs, I suspect that the albumin level was somewhat lowered. Tests of thymol turbidity and flocculation, which might have offered additional help, were not done. The symptoms and tests certainly suggest homologous serum jaundice. For several reasons I think that it had developed into subacute yellow atrophy. On admission, the liver was somewhat enlarged and during the course of the next few days it decreased in size. The downhill course was rapid — only ten days from the time of the first clinical symptoms of hepatitis until death; that is certainly a much more rapid course than we normally see with a failing liver of a cirrhotic type, in which there is a gradual loss of a few liver cells here and there. Moreover there was a rapid decrease in liver function.

I should like to postulate that there was a basis for the severity of the homologous serum jaundice in this case. If the virus of homologous serum jaundice is introduced into the body, it immediately begins to multiply (or whatever it does) in the liver. If the liver is under stress it may become more vulnerable to the virus. We know from the work done by the Department of Anesthesiology[1] that any kind of surgery taxes the liver. This man had a combined abdominoperineal operation, and then the virus was introduced. Later, he had obstruction, and another operation for that. In addition he had a period of hypotension during surgery, which also may have made the liver cells more vulnerable to the virus because of the period of anoxia that occurred. Still later he had a collection of pus. In chronic liver disease any form of infection, trauma or stress is likely to throw the liver into failure. I think that all these factors contributed to the rapid course of the disease. In summary I think he died of subacute yellow atrophy, probably caused by the homologous-serum-jaundice virus, and that he had adenocarcinoma of the rectum, diverticulosis, gallstones and cholecystitis.

DR. BRIANT L. DECKER: I saw this patient when he had the first attack of cholelithiasis; at that time he stubbornly refused to have anything done about it. An electrocardiogram was normal. If he had not had severe pain from the cholelithiasis later, he would not have come into the hospital. I told him about the rectal findings, which I thought were the more important, but he said that he would not go into the hospital for that reason. He was a rather difficult patient from the beginning. He had paroxysmal atrial fibrillation and went into cardiac failure during the postoperative course, which probably caused further insults to the liver. We thought we were lucky to discharge him from the hospital in as good condition as he was. The day the blood for the cephalin flocculation test was taken in my office, he was obviously jaundiced, but no amount of persuasion by me or by his son or family could get him to come into the hospital so we let him go home, with nursing care. He ate well and got along well for three or four days; then he began to fail rapidly. He was eventually picked up by force and taken into the hospital by ambulance, protesting all the time. I believed that he died of subacute yellow atrophy caused by homologous serum jaundice. He had a large perineal abscess, which was pretty well drained, and by the time he came into the hospital the abscess had nearly cleared up.

Clinical Diagnoses

Homologous serum jaundice.
Subacute yellow atrophy.

Dr. Perry Culver's Diagnoses

Homologous serum jaundice.
Subacute yellow atrophy of liver.
Resection of adenocarcinoma of rectum.
Diverticulosis.
Cholecystitis and cholelithiasis.

Anatomical Diagnoses

Acute hepatitis, homologous-serum-jaundice type, with marked atrophy.
Gastroduodenitis, chronic, with ulceration and hemorrhage.
Coronary-artery disease with old myocardial infarction.
Pulmonary atelectasis.
Operation: combined abdominoperineal resection of adenocarcinoma of rectum.

Pathological Discussion

Dr. Benjamin Castleman: Autopsy did show a homologous serum hepatitis. Dr. Culver called this subacute yellow atrophy rather than acute. Ordinarily, in the subacute stage, we see regenerating nodules two to three weeks after the onset, but within the first week or ten days there is not very much chance for regeneration. There was none here. There was a very marked necrosis.

Dr. Culver: I called it subacute rather than acute because, if this had been acute yellow atrophy, I do not believe that the patient would have lived for ten days. That is a matter of semantics.

Dr. Castleman: The microscopical slides of the liver showed a fulminating necrosis. He also had a bile nephrosis, which one would expect with such severe jaundice and which accounted for the oliguria at the end.

Dr. H. H. Heyl: Was there any other disease in the liver?

Dr. Castleman: No; it was completely free of other disease.

I have asked Dr. Rasmussen, the head of the blood bank, to tell us about the frequency of homologous serum jaundice in this hospital and what can be done about it.

Dr. Morten Grove-Rasmussen: The transmission of serum hepatitis by the transfusion of whole blood and plasma is still one of the major problems in blood banking. So far it has not been possible to develop methods for the detection or inactivation of the serum-hepatitis virus in whole blood or human plasma. Until this goal has been reached, I think we ought to emphasize the fact that the risk of a serious complication like serum hepatitis should always be taken into consideration before a transfusion of whole blood or plasma is started in any patient. The precautions that we are taking at the moment in the blood bank are twofold: one deals with the handling of the blood-letting instruments, and the other with the history of the donor. Syringes, needles and lancets, which can transfer the disease from one person to another, are only used for one donor or patient at a time and heat sterilized before use. The heat sterilization is either autoclaving for twenty minutes at 250°F. or boiling in water for thirty minutes.

The other precaution is a much more difficult problem. We have for the past three years in the state of Massachusetts had the rule that a donor is acceptable if he has had infectious hepatitis, under which is listed homologous serum jaundice and epidemic hepatitis, more than twelve months previously. Also, the donor is acceptable if he has not been in close contact with infectious hepatitis in his household at the time when he is giving his blood. These rules were set up in 1952 after consultation with Stokes,[2] one of the country's experts on infectious hepatitis, who at that time did not know about any case in which the convalescent serum from a person after about a twelve-month period had transferred the disease from donor to patient. The latest experience, particularly of Dr. Roderick Murray's group,[3] makes it questionable whether this rule is completely valid, or whether it has to be changed. If it must be changed we shall probably have to reject all donors who have had hepatitis of any sort in their whole lives.

No matter what time limit is set on the donors who have had known hepatitis, the problem of the more dangerous group of the donors, the asymptomatic, healthy carriers of the hepatitis virus, is not solved. Some of these persons have positive liver-function tests, but others, the so-called silent carriers, have no symptoms, never had any symptoms and do not have positive liver-function tests. So even the use of the liver-function tests on all donors to screen out carriers is not a 100 per cent safety measure.

We have followed the rules of the Massachusetts Department of Public Health for the last three years. In these three years we have given about 36,000 transfusions of whole blood. Twenty cases of serum hepatitis have been reported to the blood bank; of those 20 cases, 2 or probably 3 have been fatal, which is close to the 10 per cent average mortality of serum hepatitis. Of course, there are probably a few patients who are not readmitted to this hospital or whose hepatitis might not be reported to the blood bank. Twenty out of 36,000 is about 0.05 per cent, an extremely low rate. The average frequency of serum hepatitis after transfusions of whole blood for this country is about 0.5 per cent; the figure is higher in most of the European countries, about 1 per cent. More than half the 20 patients fell in the group of big users of blood, having received more than 5 transfusions — 5 to 20 pints of blood. It is obvious that

the possibility of transferring serum hepatitis is increased with the number of transfusions given to a patient. It is therefore worth emphasizing that the risk of serum hepatitis, which is a dangerous complication, should always be taken into consideration before another pint of blood is added to a patient's transfusion record and should be weighed carefully against the indication for the blood.

We have only one recorded case of infectious hepatitis in a patient who received plasma, besides whole blood. That patient received 20 units of blood and 4 units of plasma I think it is likely that the serum hepatitis was transferred with the whole blood since he received 20 units of that. In the same three-year period we gave out 1200 units of plasma. This is an extremely low rate for serum hepatitis after plasma transfusions. The average figure reported is anywhere from 1 to 20 per cent. The reason for our low rate, I believe, is that we make our own plasma, using 1 unit of blood for each unit of plasma. Most cases of serum hepatitis occur after transfusions of pooled plasma. The pools have contained 20 to 100 units of plasma. We prepare our plasma from 1 unit of blood and then store it for at least six months at room temperature, which should decrease the possibility of serum hepatitis and make the plasma safer than the whole blood.

The salt-free serum albumin and the plasma from which the fibrinogen and the gamma globulin have been removed, a product that is being made available by the Massachusetts Department of Laboratories, are both free of serum-hepatitis virus so far as we know. They have all been treated with heat at 60°C. for ten hours, and that is supposed to kill the virus. These products, which are plasma substitutes, will probably be made more readily available in the near future as a result of the plasma salvage program that has been started in Massachusetts.

References

1. French, A. B., et al. Metabolic effects of anesthesia in man: comparison of effects of ether and cyclopropane anesthesia on abnormal liver. *Ann. Surg.* **135**:145-163, 1952.
2. Stokes, J., Jr. Hemoglobin serum hepatitis in relation to blood transfusion. Paper presented at meeting of New England Association of Blood Bank Directors, Dec. 18, 1951.
3. Murray, R. Personal communication to Supervisory Committee on Blood Banks, Massachusetts.

CASE 41222

Presentation of Case

First admission. A twenty-four-year-old Negress, a ward helper, was admitted to the Emergency Ward because of abdominal pain of seven hours' duration.

In the midafternoon of the day of admission she noted the sudden onset of midepigastric "churning" pain, which radiated toward the right flank and was soon followed by nausea and vomiting of bile-stained fluid. The pain was persistent and noncolicky. Shortly after the onset of the pain, she passed a loose, non-watery stool. In the six hours before admission she voided three times without dysuria or burning.

There had been numerous visits to the clinic for minor complaints during the six years before entry.

Physical examination revealed a well developed, thin woman in no acute distress. The only positive findings were enlargement of several anterior cervical and submaxillary lymph nodes bilaterally and moderate tenderness in the region of the right adnexa.

The temperature was 99.2°F., the pulse 80, and the respirations 16. The blood pressure was 112 systolic, 70 diastolic.

The urine was normal. The hemoglobin was 10 gm. per 100 cc., and the white-cell count 21,000. Culdoscopy revealed normal tubes and ovaries, with no evidence of appendicitis. On the second hospital day the pain began to lessen. The patient was discharged four days later with mild tenderness in the cul-de-sac as the only residual sign or symptom.

Second admission (eight weeks later). She was readmitted to the hospital because of steady, gnawing epigastric pain and episodes of weakness and nausea of three days' duration. The pain was relieved somewhat by eating. In the interval between admissions the patient had experienced intermittent epigastric pain. There was no history of intolerance to fatty foods or gaseousness. However, the urine had become dark, and the stools light brown.

Physical examination was negative except for tenderness and spasm in the right upper quadrant of the abdomen, and questionable scleral icterus.

The temperature was 99.6°F., by rectum, and the pulse 80. The blood pressure was 100 systolic, 60 diastolic.

Examination of the blood revealed a white-cell count of 9200 and a prothrombin time of 15 seconds (normal, 14 seconds). The total protein was 7.0 gm., with an albumin-globulin ratio of 1.2, the alkaline phosphatase 8.9 units, and the bilirubin 2.7 mg. per 100 cc. The cephalin flocculation was + in twenty-four and forty-eight hours. A gastrointestinal series was normal. The patient was discharged improved on the third hospital day on a bland diet, Amphojel and sedatives.

Third admission (sixteen and a half months later). She was readmitted to the hospital with complaints of sore throat, diarrhea and right-flank pain of six days' duration.

Shortly after discharge she was asymptomatic. Liver-functions tests then revealed a bromsulfalein retention of 1 per cent and an alkaline phosphatase of 5 units, a bilirubin of 0.5 mg. and a thymol turbidity of 2.5 units per 100 cc. Seven weeks after discharge, she was admitted to the Emergency Ward for gnawing epigastric pain. The temperature was 99°F., and the white-cell count 8000, and the urine was normal. The pain disappeared after administration of 0.5 mg. of atropine subcutaneously. Four weeks later epigastric pain, ameliorated by vomiting,

and weakness recurred, and again relief was obtained by subcutaneous injection of 0.5 mg. of atropine. The patient was now two or three months pregnant. A gastrointestinal series was normal. On several later visits to the clinic there were complaints of recurrent dragging right-upper-quadrant pain. Eight months before admission, the baby was delivered at another hospital. No transfusions of blood or plasma were given to the patient.

Six days before entry a "chest cold," coryza, a sore throat and malaise developed. These were accompanied by a constant, aching right-upper-quadrant pain that was not related to intake of food. Three days later a nonproductive cough appeared, and the urine became dark. There was no anorexia or nausea. There was no history of exposure to hepatotoxins.

Physical examination was negative except for probable scleral icterus and a tender smooth liver edge 2½ fingerbreadths beneath the right costal margin.

The temperature was 101°F., the pulse 84, and the respirations 22. The blood pressure was 95 systolic, 60 diastolic.

The urine was orange, had a specific gravity of 1.024 and gave negative tests for albumin and acetone, a green test for sugar and a +++ test for bile. The sediment contained 5 to 10 white cells per high-power field. The urobilinogen was 0.5 Ehrlich units per two hours. Examination of the blood revealed a hemoglobin of 10.8 gm. per 100 cc. and a white-cell count of 12,500, with 63 per cent neutrophils, 31 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The red cells showed moderate hyperchromia and microcytosis. The serum iron was 100 microgm. per 100 cc. (normal, 125 to 200 microgm.). The prothrombin time was 15 seconds (normal, 13 seconds). Cephalin flocculation was negative in twenty-four and forty-eight hours, the thymol flocculation was ++, and the bromsulfalein retention was 59 per cent in forty-five minutes. The total protein was 7.9 gm., with an albumin-globulin ratio of 0.9, the nonprotein nitrogen 20 mg., the fasting blood sugar 93 mg., the thymol turbidity 6.0 units, the bilirubin 5 mg. direct and 6 mg. total, the alkaline phosphatase 23.4 units, the cholesterol 210 mg., and the cholesterol esters 108 mg. per 100 cc.; the sodium was 136 milliequiv., the chloride 110 milliequiv., and the potassium 4.5 milliequiv. per liter. The cholinesterase was 0.48 delta pH per hour. Two stool specimens were light yellow brown and guaiac negative. Duodenal drainage yielded a practically colorless fluid of pH 8. The sediment contained numerous leukocytes and red cells; there was no cholesterol or calcium bilirubinate. The viscosity was 1 minute and 25 seconds.

An x-ray film of the chest was normal. A plain film of the abdomen revealed a liver of normal size and a normal right kidney; the left kidney was poorly defined. The spleen was not outlined, but was apparently not enlarged. The visualized bones showed no abnormalities. A Graham test resulted in no visualization of the gall bladder. On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Allen G. Brailey*: This woman had an illness of over eighteen months' duration with many interesting and unusual features. At the time of the first study there was tenderness on the right side of the pelvis, which excited enough curiosity so that she was examined with the culdoscope, but even with its help no explanation of the pelvic tenderness was found.

The remainder of the symptoms and signs that developed over the next year and a half centered for the most part in the epigastrium and the right upper quadrant. This area, of course, includes a number of organs and parts, each of which may be the site of serious disease: the gastric antrum, the duodenum, the pancreas, the gall bladder and biliary tree, the liver and the kidney, to say nothing of the small and large bowel, which may move in and out of this area. It is not fair to hold all these organs responsible. The patient had some flank pain and a few white cells in the urine, but I see no real reason to suppose that kidney disease contributed to the illness. A gastrointestinal series was normal on two occasions so that perhaps the stomach and duodenum may be exonerated. On the other hand the liver was obviously a primary or secondary cause of the trouble.

Is there anything that you can tell us about the x-ray films that is not already in the protocol, Dr. Wang?

Dr. C. C. Wang: No.

Dr. Brailey: Is the duodenal loop enlarged?

Dr. Wang: No; it is not enlarged. There is no extrinsic or intrinsic pressure defect.

Dr. Brailey: Is there any calcium in the region of the pancreas?

Dr. Wang: I see no calcification in the pancreas.

Dr. Brailey: Is there any indication that the spleen is enlarged?

Dr. Wang: No.

Dr. Brailey: Intermittent jaundice calls to mind the possibility of hemolytic jaundice such as develops in sickle-cell anemia and in the presence of spherocytosis. The spleen, however, was not enlarged, and the serum bilirubin was able to pass the glomerular membranes so that it is a little difficult to consider hemolytic anemia seriously. I was puzzled by the degree of the anemia. The progression of symptoms could have followed in the wake of sickle-cell anemia.

The most significant signs point to trouble with the biliary system. At the time of the second admission all studies were normal except for tenderness in the right upper quadrant, slight fever and raised alkaline phosphatase and serum bilirubin. This was all evidence for common-duct obstruction. In fact I am surprised

*Assistant physician, Massachusetts General Hospital.

that a Graham test was not done at that time. The patient continued to have bouts of pain every few weeks, with epigastric discomfort and gastrointestinal irritability, and a year and a half after onset she was again jaundiced; at this time the albumin-globulin ratio had fallen, the thymol turbidity and flocculation were elevated slightly, and the cholesterol ester ratio was somewhat low. In short she had evidence of some hepatocellular damage as well as biliary-tract obstruction. Was the illness primarily due to liver-cell disease, such as infectious hepatitis or homologous serum jaundice? The evidence is all in favor of obstruction. The onset and course of the illness are not suggestive of viral hepatitis. The reported white-cell counts were too high for hepatitis. The pattern of the liver-function tests at first was typical of obstructive disease, and only after the illness had persisted for a year and a half was there evidence of liver-cell damage.

So I think that the jaundice and the liver damage were due to obstructive disease. So many things may obstruct the flow of bile that I shall begin with the commonest — namely, a gallstone in the common duct. That may prove to have been the answer, but, on the whole, it seems improbable. The patient was not the physical type, nor had she arrived at the chronologic age when gallstones are a usual hazard. Then, also, the symptoms had been intermittent and had caused jaundice that came and went. Certainly, gallstones may cause intermittent pain, — probably as they move along the cystic or the common duct, — but once a gallstone has plugged the common duct sufficiently to cause jaundice, the jaundice is commonly not relieved until the stone is removed surgically. I am sure that gallstones may cause intermittent obstruction sometimes, but they do not often do so. If all this illness is to be ascribed to gallstones, we must suppose that a first stone caused several weeks of pain and partial obstruction of the common duct and that this stone finally passed the sphincter of Oddi, a second one later producing more disability and a second attack of jaundice.

Did the patient have cholangitis? Cholangitis may be characterized by relapses and remissions of symptoms with local pain and tenderness, fever, leukocytosis, intermittent jaundice and often a marked anemia — and she was quite anemic. The liver was enlarged as it is in early biliary cirrhosis. I think she may well have had cholangitis, but again she was younger than most victims of the disease and there was no good antecedent cause such as chronic cholecystitis or biliary-enteric fistula.

I have never recognized a case of porphyria. I suspect it is often missed because it is not considered. Acute intermittent porphyria characteristically causes bouts of abdominal pain, peripheral neuropathy and psychic changes. Skin pigmentation often occurs, and porphyrins can be found in the urine if they are sought. However, in the early stages, many of these features are missing; the patients are often studied for acute abdominal surgical disease and are often called neurotic. But jaundice and frank liver disease have rarely been reported, and I do not seriously think this patient had porphyria.

Chronic interstitial pancreatitis is another indolent, inflammatory disease causing intermittent bouts of abdominal pain. It is commonly associated with biliary-tract disease. Bockus[1] comments that in two thirds of the cases chronic gall-bladder disease is associated with pancreatitis and that in about a third of the cases of pancreatitis there is disease of the biliary tract. Often, it is difficult to say where trouble began — whether in the pancreas or in the biliary system. Diabetes does not occur until the islands of Langerhans have been mostly destroyed, and, in fact, there may not be the characteristic stool changes of pancreatic disease until the gland is very badly damaged. Was there a glucose tolerance test or serum calcium determination? I judge that the serum enzyme tests were not done.

Perhaps the biliary obstruction was due to cancer of the head of the pancreas, of the ampulla of Vater or of the gall bladder itself, or it may have been due to pressure from lymphomatous glands. Duodenal drainage produced little or no bile, but there were white and red blood cells in the sediment — a finding that certainly constitutes a possible clue to neoplastic disease. Even the long and intermittent course does not exclude neoplastic disease, but it does make it seem unlikely.

I doubt if there was any great confidence about the preoperative diagnosis, but I think it was decided that it had to be determined whether the patient had a condition that could be relieved by surgical treatment. I have no confidence in what was found, but I prefer to believe that the underlying mischief was inflammatory rather than neoplastic and that it involved both the biliary tree and the pancreas.

DR. ALFRED KRANES: I wonder why Dr. Brailey so readily gave up the possibility of a hemolytic disease.

DR. BRAILEY: I think probably that should have been discussed further. Hemolytic anemia is usually associated with acholuric jaundice, which this patient did not have. It is usually associated with an enlarged spleen, which she also apparently did not have.

DR. KRANES: But many patients with hemolytic disease of one sort or another also frequently have gallstones. Were any studies on hemolysis done on this patient?

DR. EDGAR B. TAFT: None were recorded.

DR. BRAILEY: Apparently, the service did not think she had that disease.

DR. JOHN H. KENNEDY: A sickle-cell preparation was done and was negative for sickling. Electrophoresis of the patient's hemoglobin showed a pattern

consistent with sickle-cell trait but not sickle-cell disease.

DR. KRANES: Were studies of urobilinogen excretion done?

DR. TAFT: Only those reported in the protocol.

CLINICAL DIAGNOSES

Probable obstructive jaundice.
Possible infectious hepatitis.

DR. ALLEN G. BRAILEY'S DIAGNOSIS

Inflammatory disease of biliary tree and pancreas.

ANATOMICAL DIAGNOSIS

Carcinoma of head of pancreas, with metastases to lymph nodes of porta hepatis and liver.

PATHOLOGICAL DISCUSSION

DR. TAFT: The first operation that was done on this patient was a liver biopsy. The sections showed only biliary obstruction—bile plugs in the canaliculi—so that the service decided there was little that could be done to establish the diagnosis except to explore this woman. Dr. Kennedy did the operation.

DR. KENNEDY: Our preoperative diagnosis was obstructive jaundice that presumably was due to a common-duct stone. At operation this woman was found to have a carcinoma of the head of the pancreas, which had extended to involve the lymph nodes of the porta hepatis. The actual cause of the jaundice was involvement of the proximal end of the main hepatic bile duct. The liver contained multiple intrahepatic and subserosal metastases. We attempted to pass a probe into the hepatic duct through the open common duct but could not because of the carcinomatous involvement. Except that a small piece of tissue was removed for biopsy, nothing further was done.

DR. BRAILEY: I should like to ask Dr. Kennedy how often a stone causes intermittent jaundice and then is passed?

DR. KENNEDY: I think that must happen fairly frequently, for patients whom we explore with chronic cholecystitis and cholelithiasis often have a history of frequent intermittent attacks of jaundice, which we attribute to the passage of stones. That history is one of our criteria for exploration of the common duct.

DR. TAFT: It might be pointed out that this patient did not have colicky pain.

We were given one of the lymph nodes from the area of the porta hepatis, which showed large foci of necrosis as well as areas of anaplastic carcinoma. These findings would fit well with carcinoma arising from the pancreas as we thought at operation. We were somewhat dubious about presenting this case at one of these conferences because carcinoma of the pancreas is so rare before the age of thirty. Very few cases have been recorded in the literature. Willis,[2] in his book on tumors, mentions approximately 5 that were found before the age of twenty-five and which seemed to be authentic. This patient probably had tumor at the time of her second admission, suggesting that it started at the age of twenty-four.

DR. H. L. HEYL: Were any of the cases mentioned by Willis in children?

DR. TAFT: One was in a boy of fifteen, but that was the youngest that Willis had heard of. In other series none were described before the age of thirty. The usual age for this disease is the fifth or sixth decade.

REFERENCES

1. Bockus, H. L., et al. *Gastro-Enterology*. Vol. 3. 1091 pp. Philadelphia: Saunders, 1946. P. 792.
2. Willis, R. A. *Pathology of Tumours*. 992 pp. St. Louis: Mosby, 1948. P. 444.

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ANNUAL MEETING IN RETROSPECT

A PORTION of the time of the hundred and seventy-fourth annual meeting of the Council of the Massachusetts Medical Society, which, on May 16, sat from 5:00 to 11:45 p.m., with time out for supper, was spent in debating parliamentary procedure. It appeared also that some councilors, in discussing subjects having to do with the relations of the Society to hospital trustees, medical-school policies and similar matters, became preoccupied with specific problems of semantics and occasionally lost sight of the general principle that in these matters the Council is advising, recommending or simply expressing opinions rather than laying down rules that the independent agency must follow. It is probable that careful attention to these relations, developed with the sagacity for which the Council is recognized, will enhance the prestige of the Society and still further extend its influence.

The reports of the Committee on Public Relations and its Subcommittee on Medical Economics were subjected to prolonged debate. The first included the matter of the establishment of departments of general practice as part of the staff organization of general community hospitals, and the organization of district mediation committees to adjudicate minor disputes regarding physicians' services; the second dealt with the organization of home-care programs as part of the activities of medical schools and teaching hospitals.

In debating the report of the Committee on State Legislation a strong and courageous stand was taken on the ill advised bill requiring blood grouping of all patients admitted to hospitals, which has been introduced into the Legislature, and the Committee was unanimously charged with the duty of opposing it in the Legislature and carrying the Society's reasonable objections to the Governor. The action of the Committee in approving a modified version of House Bill 705, relative to the registration of nurses, was approved by the Council.

The report of the Committee on Hospital and Professional Relations relative to establishing a method by which residents in training in hospitals should be permitted to benefit by Blue Shield payments on behalf of ward patients was debated with an eloquence reminiscent of the famous cross-of-gold speech of the last century. It furnished one of the high lights of the session.

The industrious Committee on Maternal Welfare was subjected to unfortunate criticism for having presented in the *Journal*, prior to the meeting of the Council, its proposed set of Minimum Standards of Obstetric Care, which it had drawn up for the information and guidance of any physicians who might be interested. Early publication, which had been secured through the co-operation of the editor, seemed to be the most effective method of presenting these proposals to the entire membership of the Society, which might thus be given the opportunity of expressing its opinions to its councilors regarding their adop-

tion. This effort at an increased service to the Society appears to have been misinterpreted, with vehemence.

Further discussions and disagreements centered about the report of the Committee on Welfare Problems and the efforts that President Tripp had made in reaching a preliminary agreement with the Department of Public Welfare of the Commonwealth on the payment for physicians' services in hospitals. The report was finally accepted and the enlarged Committee was continued.

On the following day, at the annual meeting of the Society, its two most recent Nobel prize winners, Dr. John F. Enders and Dr. Thomas H. Weller, were presented and Dr. Fritz Lipmann, a laureate of 1953, was awarded honorary membership. Student prizes were presented to Mr. William R. Thomas, Jr., of Boston University School of Medicine, Mr. Charles S. Keevil, Jr., of Harvard Medical School, and Mr. John Q. Marshall of Tufts University School of Medicine. An increased number of fifty-year medalists were honored, the living past presidents received their newly conceived certificates of service, and the annual discourse, already published in the *Journal,* was delivered by Dr. Carl Bearse. The outstanding features of the second day were the delivery of the Shattuck Lecture, by Dr. Charles G. Child, III, and the annual dinner, with Governor Christian A. Herter as speaker.

REHABILITATION AT BOSTON UNIVERSITY

THE wars of the twentieth century, with their by-product of variously crippled minds and bodies, have been largely responsible also for the development of a new medical, surgical and social point of view within the medical profession. Spurred on by the necessities of the situation this point of view has resulted in new services for handicapped persons that have been extended to those incapacitated by the exigencies of civil life.

Rehabilitation — literally the fitting to make one's livelihood again — has been developed beyond the point of a technical specialty. It is a science and a service to make those suffering from various chronic disabilities better able to care for themselves, to live with themselves and others, and in the majority of cases to become re-employable in co-operating industry.

With the increasing role in medicine that rehabilitation has been playing, especially in the last fifteen years, various clinics and similar services have been established, some of them with the help of insurance companies, some with the help or encouragement of various government agencies. Of these the new Shattuck Hospital for the study and rehabilitation of the chronically ill, constructed and operated by the Commonwealth of Massachusetts, is one of the best equipped to carry out such purposes if its usefulness to the citizens of the State is not too greatly impaired by the pressures of political expediency.

The newest departure in rehabilitation service was announced late in April by the presidents of Liberty Mutual Insurance Company, Massachusetts Memorial Hospitals and Boston University. This is to consist of an industrial rehabilitation department and neurosurgical service for the treatment of paraplegic patients, to be constructed by Liberty Mutual as part of Haynes Memorial of the Massachusetts Memorial Hospitals. New construction will entail the rehabilitation of the east wing of the hospital to provide a unit with all the facilities necessary for 26 paraplegic patients, a neurosurgical operating room and a lecture amphitheater.

Of major importance to the success of the undertaking is the selection of Dr. Donald Munro to head the new department. Chief of neurosurgery at the Boston City Hospital, Dr. Munro has been a distinguished pioneer in the treatment of injuries of the spinal cord.

HEMISPHERIC RELATIONS

A SIGNIFICANT special article by Dr. James Howard Means, Jackson Professor of Clinical Medicine Emeritus at the Harvard Medical School, appears elsewhere in this issue of the *Journal.* Written for a particular purpose and based on two of the most important facts known to medical science — the affinity of iodine for the thyroid gland and the property of iodine of becoming radioactive — Dr. Means's paper gives the historical background of the subject and summarizes the present knowledge of radioactive isotopes in relation to the thyroid gland.

The purpose of this scientific essay was to serve as the opening address, as its footnote states, in a course on the clinical application of radioactive isotopes given at Santiago, Chile, in the fall of 1954, under the auspices of the University of Chile. The recent South American visit of Dr. Means and his associates, Dr. John B. Stanbury and Dr. Gordon L. Brownell, of which this course was a part, represented in itself a return visit to the Mendoza goiter study. This study was an outgrowth of the previous expedition of 1951, in which Dr. Douglas S. Riggs also participated, which had resulted in the Instituto del Bocio, a permanent research undertaking at Mendoza, Argentina.

Another objective of the 1954 pilgrimage was attendance of the North American group at the Third Pan-American Endocrinological Congress at Santiago, at which Dr. Fuller Albright, of Boston, was guest of honor; a final purpose was a scientific and social visit to colleagues in endocrinology in Lima, Santiago, Mendoza, Buenos Aires and Montevideo.

The specific and practical importance of such a mission in terms of mutual research and education

needs no particular emphasis; these exchanges are part of the international code of science and of culture. Their value in strengthening a general hemispheric amity and understanding transcends the purely intellectual relations, important as they are.

JULY 15 DEADLINE

NEARLY four months ago this column contained one of the earliest intimations revealed in New England that the American Medical Association will go on location in the area next November. Since that announcement was published the multiplying local committees, the general chairman, the general co-chairman, the division chairmen responsible respectively for program, television and entertainment, and the New England States representatives have been working far into each night.

One of the results of their efforts, of paramount importance and immediate concern, relates to the papers that will be presented at the meetings of the Clinical Session, November 29 and 30 and December 1 and 2. The important point in this respect is that, whereas all fellows of the Association are invited to offer papers for presentation at the meetings, certain conditions must be observed.

Most important of these is that abstracts of the proposed papers, limited to a 300-word summary including vital data and conclusions, must be submitted *in duplicate* to the chairman of the Program Committee, A. M. A. Clinical Session, 22 Fenway, Boston 15, Massachusetts, before July 15, 1955. This relative deadline is softened only to the point of becoming an absolute deadline on August 1, 1955, and not a moment beyond. It will not, however, be a matter of first come, first served. All abstracts will be reviewed not only by the Program Committee but, if necessary, by experts in the several special fields, and final selections will be on a purely competitive basis.

All papers presented at the session must be original contributions that have not previously been presented or published, they may relate to the clinical, scientific and investigative aspects of all branches of medicine and surgery and, having been accepted for presentation, they become the property of the American Medical Association.

The above points of information, encouragement, guidance and warning have been confirmed by recent dispatches from the headquarters of the Association, which announce also that applications for space in the Scientific Exhibit are now available and will be sent on request. These exhibits, which will supplement the lectures as far as possible, should portray subjects of a broad general interest. Requests for applications should be sent to the Secretary, Council on Scientific Assembly, American Medical Association, 535 North Dearborn St., Chicago 10, Illinois.

The Woman's Hospital in New York has been opened at No. 83 Madison Avenue, for the reception of patients, and Dr. J. Marion Sims has sufficiently recovered his health to engage in the medical and surgical department of this charity.
Boston M. & S. J., *June 7, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

AMNIOTIC-FLUID EMBOLISM

A thirty-two-year-old gravida I, para O, with an uneventful prenatal course, went into spontaneous labor at term. The eight-hour labor was uneventful, and the fetal heartbeat was heard two hours before delivery. Demerol, 75 mg., was given an hour and a half before delivery when the cervix was dilated 3 fingerbreadths. There was no respiratory difficulty, cyanosis or shock during labor. The membranes ruptured spontaneously about twenty minutes before delivery. Under ether anesthesia a stillborn infant was delivered, but the cause of the stillbirth was not apparent. There was no difficulty with the anesthesia. A small second-degree laceration of the perineum was sutured, and the placenta was delivered after twenty minutes. Blood loss was not described, but the fundus was boggy, and the patient apparently continued to bleed freely. The blood was watery and did not clot. Oxygen and oxytocics, 300 cc. in 5 percent dextrose in water, were given, but the patient gradually slipped into profound shock. After considerable delay, a consultant saw the patient, finding the uterus soft and halfway to the umbilicus. The radial pulse was absent, and the blood pressure was not obtainable. He thought she had afibrinogenemia and recommended transfer to a municipal hospital. On arrival, there was no pulse or respirations, and the blood pressure was not obtainable. Epinephrine and Coramine were given immediately, and a pulse was obtainable for a few minutes. She was pronounced dead seventeen minutes after arrival, three hours and fifteen minutes after delivery. Autopsy showed amniotic-fluid embolism, with no laceration or rupture of the uterus but with moderate hemorrhage into the placental site for a depth of 1 cm. over an area 5 or 6 cm. in diameter. This apparently was the portal of entry for the fluid.

This was classified unanimously as a preventable death, the primary cause being hemorrhage. The secondary cause was, of course, afibrinogenemia. This, in turn, obviously was the result of amniotic-fluid embolism.

Although such an embolism is not entirely preventable today, its results need not necessarily be

fatal since hemorrhage alone in a modern hospital can easily be corrected by transfusion. Similarly, afibrinogenemia can be corrected by the infusion of fibrinogen. To be sure, this substance is not available in all hospitals, but it most certainly is in the larger centers. In the case under discussion hemorrhage became apparent at the time the placenta was expressed, but the patient did not arrive at the municipal hospital until she was practically dead. The intervening period of more than two hours would have allowed ample fibrinogen and blood to be administered to the patient, although it is realized that this is not so easy as it sounds; it is nevertheless possible and should have been attempted.

There is a popular opinion in the medical profession at present that amniotic-fluid embolism is a completely fatal and completely nonpreventable cause of death. This is true only when the embolization is absolutely overwhelming. Obviously, it was not overwhelming in this case, as attested by the patient's clinical course and as later proved by autopsy.

JOHN FIGGIS JEWETT, M.D.
Chairman

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

ORTHOPEDIC CLINIC	DATE	CLINIC CONSULTANT
Haverhill	June 1	William T. Green, M.D.
Greenfield	June 2	Charles L. Sturdevant, M.D.
Lowell	June 3	Albert H. Brewster, M.D.
Salem	June 6	Paul W. Hugenberger, M.D.
Gardner	June 7	Carter R. Rowe, M.D.
Brockton	June 9	George H. Van Gorder, M.D.
Lynn*	June 13	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Pittsfield	June 15	Edward J. Coughlin, Jr., M.D.
Worcester	June 17	John W. O'Meara, M.D.
Fall River	June 27	David S. Grice, M.D.
Springfield	June 28	James D. Fisher, M.D.
Hyannis	June 30	Paul L. Norton, M.D.

RHEUMATIC-FEVER CLINIC	DATES
Fitchburg	June 1, 8, 15, 22, 29
North Reading	June 7, 14, 21, 28

PLASTIC CLINIC	HELD	CONSULTANT
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

CORRESPONDENCE

TELEVISION PROGRAM AT A.M.A. CLINICAL SESSION

To the Editor: Physicians of New England are showing a most gratifying spirit of co-operation in the early planning for the Clinical Session of the American Medical Association to be held in Mechanics Building, Boston, for the four days from November 29 to December 2, 1955. One feature of the session will be the television programs (in color), which will be possible through the generosity of Smith, Kline and French Laboratories of Philadelphia.

Television programs will originate from the New England Deaconess Hospital and will be sent by closed circuit to a special hall in Mechanics Building. The morning programs will be *surgical*, demonstrating operations by surgeons on the staff of the Hospital. The afternoon programs will consist of talks, demonstrations and panel discussions on *medical* subjects.

Participation in the afternoon medical programs is open to all, subject to acceptance by the Television Committee. Physicians desiring to take part are urged to send promptly abstracts summarizing the proposed presentation in not more than 300 words. In addition ideas or suggestions for appropriate topics and participants in either the surgical or the medical program will be welcomed by the Committee. Prospective participants should keep in mind that a successful television demonstration *must* have visual interest. One must avoid reading a paper before the camera, and the presentation should be built around patients, instruments, apparatus, charts, slides and x-ray films. There will be no facilities for showing motion-picture films. Participants will be given information on television appearance and on size and colors of charts and slides at a special orientation meeting, which will be held six or eight weeks before the meeting.

Proposals and suggestions should be sent to the chairman of the Television Committee, Alexander Marble, M.D., 81 Bay State Road, Boston 15.

C. CABELL BAILEY, M.D.
ALEXANDER MARBLE, M.D., *Chairman*
KENNETH W. WARREN, M.D.
Television Committee
Massachusetts Medical Society
Boston

MEMORIAL TO DR. SCHLESINGER

To the Editor: Sadness and a sense of personal loss gripped the New England Society of Pathologists assembled at the Beth Israel Hospital of Boston on January 20, 1955, upon the announcement that its host of the day, Monroe J. Schlesinger, had suddenly died during the afternoon recess. There was poignancy to the circumstances surrounding his final hours. He had just sat in the audience among his friends and colleagues listening to his own paper ("Focal Myocytolysis of the Myocardium"), the last of the afternoon session, as it was read by the junior author.

Monroe Schlesinger was born in New York City on June 20, 1892. His early interest was in bacteriology. He came to Boston in 1917 as one of a group of brilliant young men gathered by Professor Rosenau in what was then the Department of Preventive Medicine, the forerunner of the present Harvard School of Public Health. He earned his Ph.D. in bacteriology from Harvard in 1920. During the period from 1917 to 1922 he was intimately associated with Dr. Bronfenbrenner. Because of the location of his work in the Medical School he became impressed by the challenges and opportunities in medicine, and he entered Harvard Medical School, graduating magna cum laude with the Class of 1926. While a medical student he also worked for Professor Wolbach on rickettsial diseases as a research assistant in pathology. He took his resident training at the Peter Bent Brigham and the Children's hospitals and, in 1929, became the first pathologist to the new Beth Israel Hospital in Boston. Throughout the years he taught pathology at Harvard Medical School, attaining the rank of clinical professor in 1952. He was one of the initial members of the New England Society of Pathologists and its president in 1949-50.

For many years Dr. Schlesinger suffered from episodes of emotional depression. He struggled hard to create a front behind which to hide his distress, succeeding in this toward all except a few intimates. The length of his work year was appreciably shortened by these inactivating episodes, but during the rebound of recovery he made good the lost time by an enormous energy and by a profusion of ideas, suggestions and projects.

Four years before his death a small cerebral accident left him with impairment of his working right hand, and soon thereafter he was stricken by a nearly fatal attack of myocardial infarction. He tried valiantly to raise himself above the ever-increasing congestive heart failure and the pains of angina pectoris, to disregard the uncertainty of living on borrowed time and to continue as best he could with his responsibilities as departmental administrator, teacher and investigator. As time went on he became increasingly troubled by agonizing abdominal pains, which he himself, after months of unrelieved suffering, finally diagnosed correctly as lead colic. (For fifteen years he had been exposed to lead acetate in the preparation of a radiopaque mass for the injection and dissection of the coronary arteries, a procedure that became known as the Schlesinger technic.)

Monroe Schlesinger was a scholar of exceptional gifts. However complex and complicated his mind, his skillful hands created technics of exceptional simplicity and effectiveness. He investigated many topics in bacteriology, immunology and pathology, but became best known for his injection studies on the coronary-artery circulation that were instrumental in establishing a whole school of pathological and clinical thought. When he was stricken with lead colic the results of five years of work on a simplified injection mass were discarded, and, sick as he was, he began all over again to substitute a nontoxic radiopaque substrate for the lead compound previously employed.

He was indefatigable in research, always aiming at total rather than at partial answers. He insisted on self-discipline as a prerequisite in research. By precept he taught his pupils the enthusiasm of accuracy and the attention to detail that, in his hands, turned the smallest observation into a vehicle for fundamental concepts.

His was an incisive mind, analytic to the point of destructiveness. Although the kindliest of men he could become a scathing critic in matters of research. His thinking was unconventional. Everything he investigated, the casual as well as the planned, was approached with a singular freshness, and with attitudes most unexpected even to the initiated. He was forever curious about phenomena. Every one of his students heard him say that there was no day on which he should not discover something never seen or never appreciated before, even in the most ordinary of appendixes.

He was a superb and inspiring teacher, being at his best with individuals or small groups. He taught his pupils that pathology was not a matter of pictorial associations and of ribbon matching. He taught them not to remain satisfied with the phenomenology of a subject but always to question why and how it got that way. He taught pathology in dynamic terms and by functional concepts that, even in fixed tissue sections, emphasized the fleeting glimpse of the movie camera rather than the static quality of the still picture.

A little over a year before his death he was honored on the occasion of the twenty-fifth anniversary of his association with Beth Israel Hospital. Contributions poured in for the establishment of a Monroe J. Schlesinger Lectureship in Pathology. Together with this lectureship he was presented with a bound volume of personal letters from his friends, colleagues and pupils. This volume he came to cherish more than any other gift he had ever received. Like a leitmotiv these letters bared the character traits that had endeared him to all, however casual their contact: his selflessness, his understanding, his wise counselling, his sincerity and his integrity. They expressed the ever-recurring theme of gratitude and intellectual indebtedness — by the fledgling researcher for inspiration and guidance, by his contemporaries for his sound criticism and by the outsider for the prestige he had lent to the scientific standing of his hospital.

The letters of two "outsiders" tell the story more objectively. Dr. Paul D. White acknowledged not only "admiration of your work and of your character and my appreciation for the help you have given me through your writings, but also my affection for you as a person. Through you more than through anyone since the days of Heberden and Herrick I have learned some of the secrets about coronary heart disease. Certain mysteries of a generation ago have been cleared by your skillful and painstaking technics." And S. Burt Wolbach, his teacher and mentor, welcomed the opportunity to be able to say by letter "things that ordinarily one doesn't say to persons one respects and admires. Your proof that adequate anastomotic circulation could develop while the coronary arteries were undergoing closure will always remain as an outstanding contribution and one that should call attention to the desirability of a continuous regimen of exercise as one grows older, in order to create the demand for the development of adequate collateral circulation. Personally I am grateful, because I have felt justified in doing all the things by way of exercise that are usually condemned for a person of my age." Dr. Wolbach, then seventy-three years of age, closed the letter to his pupil, as follows: "I know you well enough to believe that your satisfactions have come from jobs superbly done and without awareness of personal sacrifices. It should also be a source of satisfaction to you that all of us, and I speak for many who have known you well, have held you in high respect as a person and as a scientist."

SIDNEY FARBER, M.D.
LEOPOLD REINER, M.D.
SHIELDS WARREN, M.D.
New England Society of Pathologists
Boston

BOOK REVIEWS

The Fundamentals of X-ray and Radium Physics. By Joseph Selman, M.D., director, School for X-ray Technicians, Tyler Junior College, chief of radiology, Mother Frances Hospital, director, Radiology Department, Medical Center Hospital, and consultant in radiology, East Texas Tuberculosis Hospital, Tyler, Texas. 8°, cloth, 340 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $8.50.

This book is simply but expertly written to explain the theory of x-ray and radium physics and their practical applications to every-day x-ray problems. This text is primarily intended for x-ray technicians. The author proceeds on the assumption, usually true, that the student technician has had practically no training, or at the most very poor preparation in basic physics, mathematics and chemistry. Starting with simplified mathematics he proceeds to discuss energy, matter, electricity, magnetism, electromagnetism, generators and motors, x-rays and x-ray circuits and, lastly, radium and radioactivity. There are also well written chapters on the darkroom and developing, x-ray film, intensifying screens and the factors in radiographic quality. A section on protection in radiology is also included. The volume is generously supplied with excellent diagrams, charts and illustrations that are easy to interpret. Terminology and application of technical terms are well explained. The author cleverly uses repetition and review throughout the book, and thus enhances the necessary didactic teaching.

Although this book is written and intended for student x-ray technicians, it can be recommended to radiology residents and candidates desiring a quick but adequate review for board examinations, as well as to physicians who desire preliminary study of basic x-ray and radium physics in preparation for work with radioactivity and isotopes in medicine.

SEYMOUR R. SHALEK, M.D.

Introduction to Psychiatry. By O. Spurgeon English, M.D., and Stuart M. Finch, M. D. First edition. 8°, cloth, 621 pp. New York, New York: W. W. Norton and Company, Incorporated, 1954. $7.00.

The name of Dr. O. Spurgeon English is well known to readers of current psychiatric books. This new volume, written with Dr. Stuart W. Finch, is comprehensive and concise. Psychiatry is a field that is constantly changing, and textbooks written only a few years ago quickly become dated. For example, the changes in the method of giving electroshock therapy, as practiced by Dr. Leo Alexander and others, are not yet widely known and have improved since Dr. Alexander's book was published two years ago. This book, with remarkable precision, outlines the entire field of present-day psychiatry, beginning with concepts of dynamic psychiatry and carrying on through child psychiatry, psychoneurotic disorders and personality disorders, until all classes of human mental ills have been touched upon. Particularly

valuable is the last chapter (in three sections) on therapy. Obviously, the authors have spent a great deal of time considering and formulating their views and those of others. The bibliography, for example, covers nearly 20 pages and is carefully selected. Now that psychiatry is seemingly everybody's business, this book will appeal to a wide audience, offering much condensed and well presented information.

MERRILL MOORE, M.D.

Atlas of Orthopedic Traction Procedures. By Carlo Scuderi, M.D., M.S., Ph.D., clinical associate professor of surgery, University of Illinois College of Medicine, professor of surgery, Cook County Graduate School, attending surgeon, Cook County Hospital, chairman, Department of Orthopedic Surgery, St. Elizabeth's and Columbus hospitals, senior orthopedic surgeon, Alexian Brothers' and St. Anne's hospitals, consulting orthopedic surgeon, Augusta Hospital, Chicago, and consulting orthopedic surgeon, McNeal Memorial Hospital, Berwyn, Illinois. 4°, cloth, 230 pp., with 124 illustrations. St. Louis: C. V. Mosby Company, 1954. $12.50.

There has long been a need for a volume such as this. Many of the illustrations and instructions about the various types of traction commonly used by orthopedic surgeons are buried in medical writings of the last fifty years. This book offers all the pertinent information in one small volume. Each type of traction is illustrated both by photographs and by line drawings. Each is accompanied by a short but adequate description of the procedure. This is an excellent book for the teaching of procedures for orthopedic traction. It should be of immense value to the industrial and orthopedic surgeon in the more efficient use of such types of therapy.

JOHN G. KUHNS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Intern's Manual (Cook County Hospital). By Arthur Bernstein, M.D., assistant medical superintendent, Cook County Hospital, and clinical associate professor of medicine, University of Illinois College of Medicine. 12°, paper, 292 pp., with 13 figures. Chicago: Year Book Publishers, Incorporated, 1954. $3.00.

The Cook County Hospital in Chicago is a 3400-bed institution. Since 1945 mimeographed instructions have been used by interns and members of the staff. They are now printed for the information of other hospitals.

The Rauwolfia Story: From primitive medicine to alkaloidal therapy. 12°, paper, 63 pp., with illustrations. Summit: Ciba Pharmaceutical Products, Incorporated, 1954. Free.

This pamphlet tells the story of the Rauwolfia root, named *Rauwolfia serpentina,* after its discoverer, and the successful isolation of the pure alkaloid reserpine and its use as a tranquilizer-antihypertensive agent in hypertension, geriatrics, gynecology and psychiatry.

Hugh Roy Cullen: A story of American opportunity. By Ed Kilman and Theon Wright; illustrated by Nick Eggenhoffer. 8°, cloth, 376 pp. New York: Prentice-Hall, Incorporated, 1954. $4.00.

This is an interesting biography of a rich Texas oilman who has given away $160,000,000 for philanthropic purposes.

Fluid and Electrolytes in Practice. By Harry Statland, M.D., associate in medicine, University of Kansas School of Medicine, consultant in medicine, Veterans Administration Hospital, and attending physician, Menorah Medical Center, Kansas City, Missouri. 8°, cloth, 206 pp., with illustrations. Philadelphia: J. B. Lippincott Company, 1954. $5.00.

This book is based on a series of lectures given in 1950 to students at the University of Kansas School of Medicine. The text is in two parts — general principles and applications to special conditions. The first is physiologic, dealing with depletions, imbalance, acid-base balance, treatment of major depletions and edema and diuretics and water intoxication. The second discusses heart, kidney and urologic diseases, diabetic acidosis, pediatric fluid balance, burns, cirrhotic ascites and toxemias of pregnancy. There is a bibliography of 161 references, as well as a good index.

NONCLINICAL NOTES

JOHN PHILLIPS MEMORIAL AWARD

Dr. George W. Thorn, physician-in-chief at Peter Bent Brigham Hospital and Hersey Professor of Medicine at Harvard Medical School, received the John Phillips Memorial Award for outstanding contribution to the progress of internal medicine, at the thirty-sixth annual session of the American College of Physicians in Philadelphia.

DIRECTOR OF HEALTH AT TUFTS UNIVERSITY

Dr. Clark W. Heath, associated for a number of years with the Department of Hygiene of Harvard University, has been appointed director of health services at Tufts University, beginning his duties in September. Dr. Heath has also been appointed to the Department of Medicine at Tufts University Medical School and to the associate staff of the New England Medical Center.

SCHERING AWARD WINNER

Marvin Jerome Friedenberg, a fourth-year student at Tufts University Medical School, has won a first prize in the ninth Schering Award Competition. Mr. Friedenberg has won a prize of $500 with an Essay on "Androgen Therapy in the Female."

NOTICES

ANNUAL CHAPLAINS' CONFERENCE

The annual Chaplains' Conference, sponsored by the New England Medical Center and the Massachusetts Council of Churches, will be held in Posner Hall, Tufts University School of Medicine, Boston, on June 20.

The conference will be held in honor of Dr. Joseph Hersey Pratt for the pioneer work in group therapy that he started fifty years ago. The program is as follows (starting at 10 a.m.):

Group Therapy and Hospital Chaplains. The Reverend Leicester R. Potter, presiding.

Group Therapy and Related Professions. Dr. Paul E. Johnson, presiding; Drs. Elvin Semard, Leo Berman and Kenneth Benne.

Banquet. Posner Hall. Dr. Joseph H. Kaplan, presiding.

History and Development of Group Therapy. Dr. Samuel B. Hadden, University of Pennsylvania School of Medicine.

Members of the medical and related professions are invited. Information and reservations may be obtained from Chaplain Haldean S. Lindsey, New England Medical Center, 171 Harrison Avenue, Boston 11, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

JUNE 5. American College of Chest Physicians. Page 553, issue of March 31.
JUNE 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.
JUNE 6–10. Woman's Auxiliary to the American Medical Association. Page 647, issue of April 14.
JUNE 6–30. Consultation Clinics for Crippled Children in Massachusetts. Page 963.
JUNE 7–9. United States Public Health Service Medical-Officer Examinations. Page 509, issue of March 24.
JUNE 8 and 15. Boston State Hospital Psychiatry Seminar. Page 461, issue of March 17.
JUNE 10–12. American Electroencephalographic Society. Page 647, issue of April 14.
JUNE 13–15. American Neurological Association. Page 689, issue of April 21.
JUNE 13–17. European Rheumatology Congress. Page 742, issue of April 28.
JUNE 20. Annual Chaplains' Conference. Page 965.
JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.
JULY, AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.
JULY 1–4. International College of Surgeons. Page 828, issue of May 12.
JULY 10–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.
JULY 11–15. Symposium on Tuberculosis. Page 509, issue of March 24.
AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.
OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association. Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JUNE 9

THURSDAY, JUNE 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Thoracic Conference. Local Factors in the Distribution of Pulmonary Blood Flow. Dr. James L. Whittenberger. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, JUNE 10

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, JUNE 11

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten and staff. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Thibodeau and staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, JUNE 13

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:30–11:30 a.m. Child Psychiatry Staff Conference. Burnham Memorial Hospital for Children (Burnham 7), Massachusetts General Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Therapeutic Conference. Dr. McCombs, moderator. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Case Reports. Dr. Burnap. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, JUNE 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. New England Deaconess Hospital.
*4:30–6:00 p.m. Anesthesia Conference. Dr. Etsten and staff. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, JUNE 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Bone and Joint Problems in Mental-Hospital Practice. Dr. Richard A. Bragdon. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry. Drs. Sullivan, B. Selverstone and Hope. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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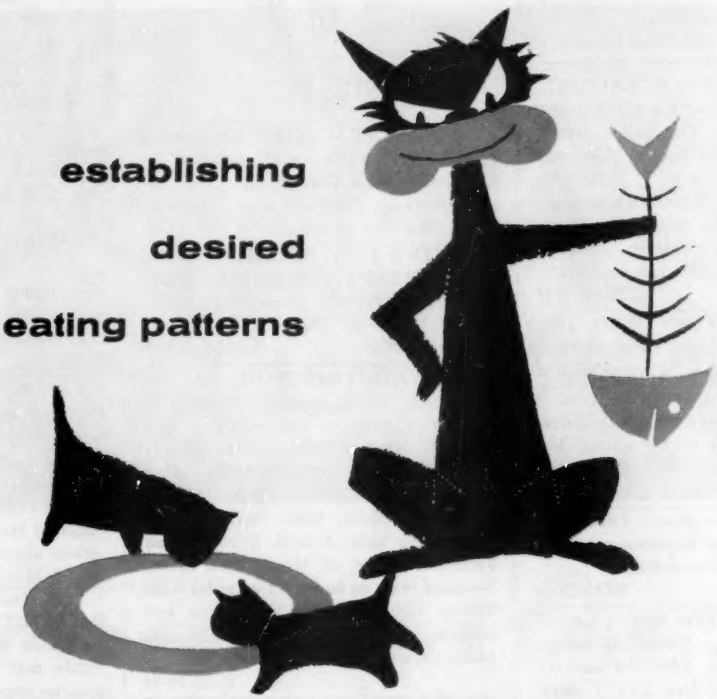

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1. Eisfelder, H. W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954.
2. Sebrell, W. H., Jr.: J.A.M.A., 152:42 (May) 1953.
3. Sherman, R. J., M.D.: Medical Times, 82:107 (Feb.) 1954.

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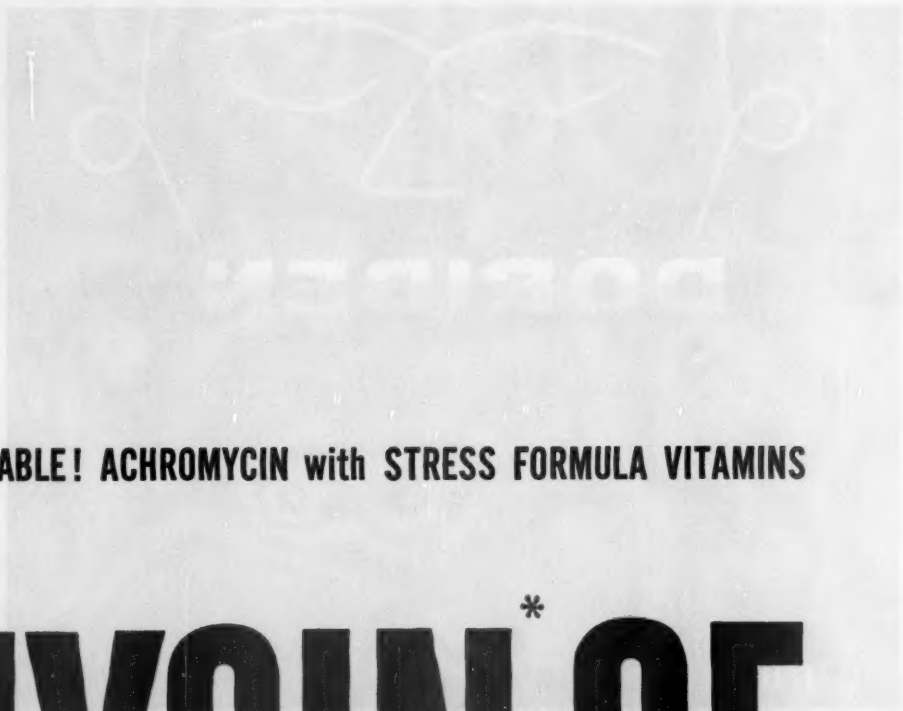

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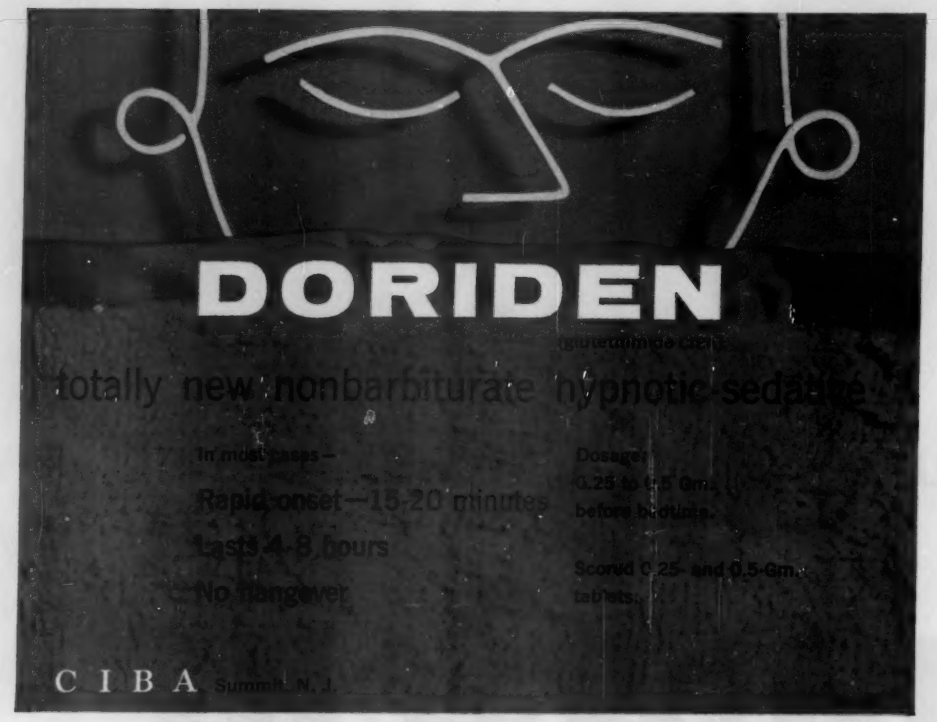

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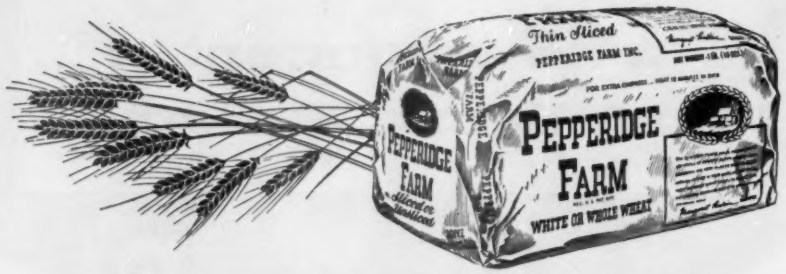

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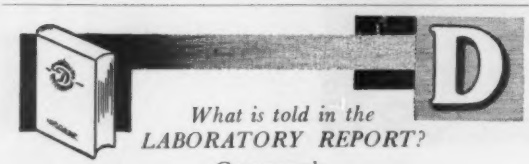

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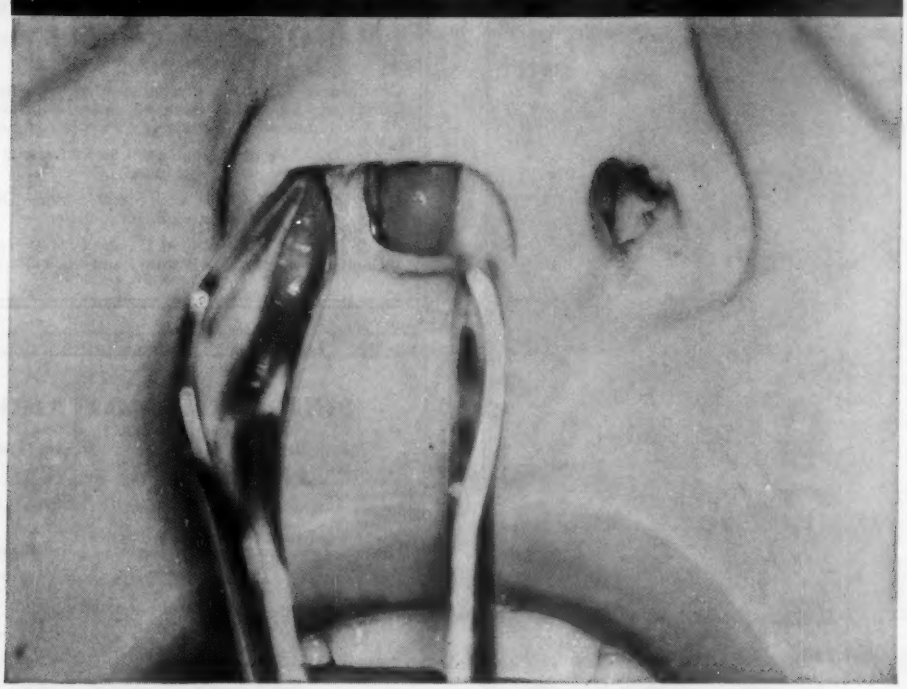

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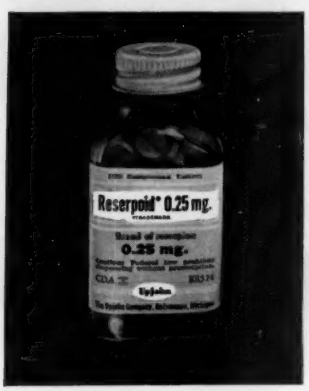

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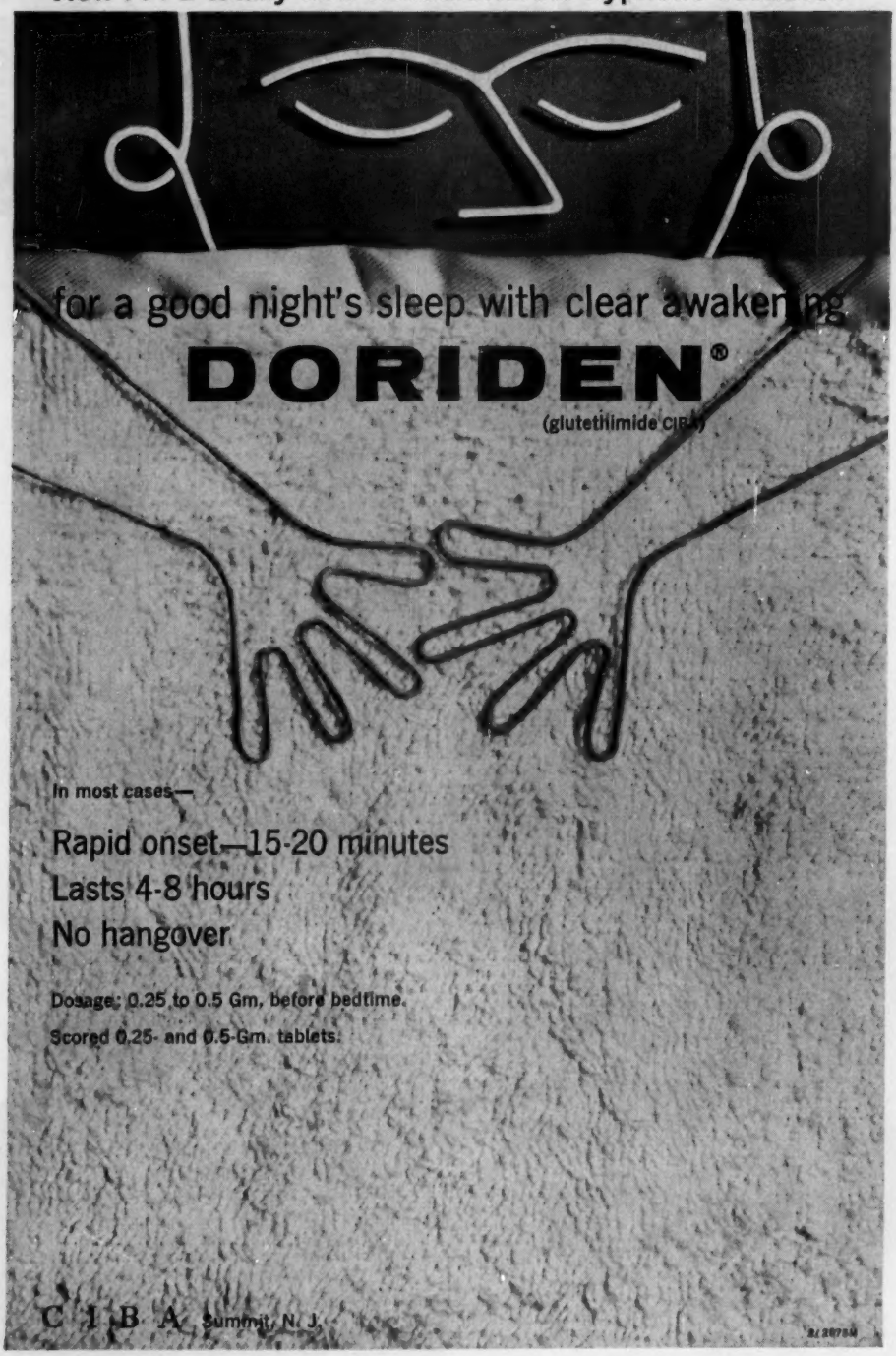
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